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(54) Title: SPLICE VARIANT OF HUMAN SODIUM III CHANNEL (HNAIII18)

(57) Abstract: Described herein is a splice variant of the human NaIII channel α subunit, designated hNaIII18. Also described are nucleotide and amino acid sequence for hNaIII18, oligonucleotide primers and probes for hNaIII18, hNaIII18 regulatory sequences, hNaIII18-specific antibodies, methods of detecting hNaIII18 proteins or nucleic acids, and methods of screening for modulators of hNaIII18 expression or activity.

Splice Variant of Human Sodium III Channel (hNaIII18)

This application claims priority from U.S. Provisional Application Serial No. 60/431,794, filed December 4, 2002, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to a human splice variant of the voltage-gated sodium III channel, termed hNaIII18, as well as methods for stable expression of hNaIII18 in cell lines, and methods of use in screening for compounds that modulate sodium channel activity.

BACKGROUND OF THE INVENTION

Sodium channels are voltage-gated transmembrane proteins that are involved in the generation of action potentials in electrically excitable cells such as neurons and muscle cells. They are responsible for the cellular uptake of sodium during electrical signals in cell membranes. The channels are members of a multigene family of transmembrane proteins and are typically composed of a large transmembrane pore-forming α-subunit and three smaller accessory β-subunits (Cattrall et al., Adv Neurol 1999; 79:441-56). The primary structure of α-subunits is conserved among different sub-types and species. The α-subunit is all that is required for the channel to be fully functional, however, the β-subunits have been shown to modulate the function of the channel. Specifically, co-expression of rat β1, β2, and β3 subunits with the Na(v)1.2a α-subunits in the tsA-201 sub-clone of HEK293 cells shifted sodium channel activation and inactivation to more positive membrane potentials. The β3 subunit alone caused increased persistent sodium currents. (Qu et al., Mol Cell Neurosci 2001;18(5):570-80).

Previous studies have demonstrated numerous different types of α-subunits, which are categorized based on their sensitivity to tetrodotoxin (a toxin produced by the puffer or fugu fish). Subunits that are inhibited by nanomolar concentrations of tetrodotoxin are generally referred to as tetrodotoxin-sensitive channels (TTX-S), while those that require at least micromolar concentrations for inhibition are referred to as tetrodotoxin-resistant channels (TTX-R).

Rapid entry of sodium ions into cells causes depolarization and generation of the action potential. Such entry of sodium ions through sodium channels in response to a voltage change on the plasma membrane in excitable cells plays a functional role in control of neuronal excitability in the central nervous system (CNS) and peripheral nervous system (PNS).

An increase in the rate of spontaneous firing in neurons is often observed in peripheral sensory ganglia following nerve injury (Ochoa and Torebjork, Brain1980; 103(4):835-53.; Nordin et al., Pain 1984; 20(3):231-45; Matzner et al., J Neurophysiol 1994;72(1):349-59; Woolf, Drugs 1994; 47 Suppl 5:1-9; discussion 46-7). It has been suggested that this hyperexcitability in neurons is due to altered sodium channel expression in some chronic pain syndromes (Tanaka et al., Neuroreport 1998; 9(6):967-72). Increased numbers of sodium channels leading to inappropriate, repetitive firing of the neurons have been reported in the tips of injured axons in various peripheral nervous tissues such as the DRG, which relay signals from the peripheral receptors to the central nervous system (Waxman and Brill, Biophys J 1978; 21(2):147-60; Devor et al., Neurosci Lett 1989;102(2-3):149-54; Matzner and Devor, Brain Res 1992; 597(1):92-98). Transcripts encoding the αIII subunit, which are present at only very low levels in control DRG neurons, are expressed at moderate to high levels in axotomized DRG neurons together with elevated levels of αI and αII mRNAs (Waxman et al, Brain Res Mol Brain Res 1994; 22(1-4):275-89). Conversely, transcripts of sodium channel α subnits in the sensory nervous system are down-regulated in DRG neurons following axotomy (Dib-Hajj et al., Proc Natl Acad Sci U S A. 1996; 93(25):14950-4). Furthermore, the partial efficacy of sodium blocking agents is well documented in patients treated for neuropathic pain (Omana-Zapata et al., Pain 1997; 7 2(1-2):41-9; Rizzo, J Neurophysiol 1997; 77(1):236-46), providing an important link between increased sodium channel expression and

neuropathic pain. Therefore, alterations in sodium channel expression and subsequent function may be a key molecular event underlying the pathophysiology of pain after peripheral nerve injury.

The partial type III isoform (α-subunit) of the human sodium channel gene, SCN3A, isolated from placenta, was first described by Malo et al. (Proc Natl Acad Sci U SA 1994; 91(8):2975-9; GenBank Accession No. S69887). Two alternative isoforms, neonatal and adult forms, of SCN3A were thereafter identified in human brain tissue by Lu and Brown (J Mol Neurosci 1998;10(1):67-70; GenBank Accession Nos. AF035685 and AF035686, respectively). These isoforms contained a 92 amino acid insert within a region containing putative splice sites (identified through sequence homology with the rat type III brain sequence). The complete coding sequences for human SCN3A genomic DNA and mRNA (and the corresponding protein sequence) also cloned from human brain, was described by Clare et al. (Ann NY Acad Sci. 1999;868:80-3; GenBank Accession Nos. AJ251507 (SEQ ID NO: 3-Figure 3) and AF225987 (SEQ ID NO: 4-Figure 4, respectively).

Most recently, in 2000, Jeong et al. submitted to GenBank an mRNA sequence encoding a splice variant of human SCN3A (Accession No. AF225987; SEQ ID NO: 5-Figure 5). The amino acid sequence of this splice variant contained a 49-amino acid insert from residues 624 to 673 (SEQ ID NO: 6 - Figure 6), when compared with the sequence described by Clare et al. (*supra*).

There remains a need in the art to identify and characterize additional human sodium channels and variants thereof, in order to assist in the identification of drug candidates that can be used to treat conditions involving or associated with over- or under-expression, or over- or under-activated sodium channels.

SUMMARY OF THE INVENTION

The present invention provides a novel splice variant of human sodium channel III α subunit, designated herein as "hNaIII18", having the amino acid sequence of SEQ ID NO: 2 (Figure 2).

The present application also provides an isolated nucleic acid having a nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 2. In one embodiment, the nucleic acid has the nucleotide sequence of SEQ ID NO: 1 (Figure

1). In another embodiment, the nucleic acid has a nucleotide sequence that is a degenerate variant of SEQ ID NO: 1. In yet another embodiment, the invention provides an isolated nucleic acid that hybridizes under stringent conditions to a nucleic acid having the nucleotide sequence of SEQ ID NO: 1, and preferably encodes a protein having the same function as a protein having the amino acid sequence of SEQ ID NO: 2.

The isolated nucleic acid encoding hNaIII18 can be a part of a recombinant vector, *e.g.*, for cloning, expression, and/or expansion. An expression vector comprises the nucleic acid encoding hNaIII18 operably associated with an expression control sequence. The invention further provides host cells containing such a vector, and methods for producing the hNaIII18 subunit polypeptide using such host cells.

In addition, the invention provides an isolated nucleic acid oligonucleotide, such as a primer or probe, of at least 10 bases, more particularly of at least 20, and more particularly of at least 30 bases, which oligonucleotide has a nucleotide sequence identical to a corresponding nucleotide sequence of the same number of contiguous bases in SEQ ID NO: 1, or its complement, which nucleotide sequence is unique and specific to the nucleotide sequence of SEQ ID NO: 1, and/or different from corresponding oligonucleotide sequences encoding known sodium channel subunits. The invention also provides an antibody that preferentiallyh binds the hNaIII18 subunit protein of the invention compared to other known sodium channel subunits.

The present invention further provides a method for detecting expression of hNaIII18 in a cell or sample derived from a cell, which method comprises: (i) detecting mRNA encoding hNaIII18 in a cell or in a sample derived from a cell suspected of expressing hNaIII18; or (ii) detecting hNaIII18 protein in a cell or in a sample derived from a cell with an antibody of the invention.

The present invention further provides an assay system for identifying modulators of hNaIII18 subunit containing sodium channels. The assay system comprises at least one cell genetically engineered to express or overexpress hNaIII18 as part of a functional sodium channel, which can be used to screen for and thereby identify modulators of a hNaIII18-containing sodium channel. In a preferred

embodiment, cells useful in conducting the assay are mammalian cells useful in such screening methods including, *e.g.*, human embryonic kidney cells such as HEK293 cells, or cells such as *Xenopus* cells

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the cDNA sequence of hNaIII18 of the present invention.

Figure 2 shows the amino acid sequence of hNaIII18 of the present invention.

Figure 3 shows the cDNA sequence of human SCN3A of Clare et al. (*supra*) (GenBank Accession No. AJ251507).

Figure 4 shows the amino sequence of human SCN3A of Clare et al. (*supra*) (GenBank Accession No. AJ251507).

Figure 5 shows the cDNA of a human sodium channel α-subunit variant by Jeong et al. (GenBank Accession No. AF225987).

Figure 6 shows the amino acid sequence a human sodium channel α-subunit variant by Jeong et al. (GenBank Accession No. AF225987).

Figure 7 shows a cDNA alignment of the hNaIII18 of the present invention, with that of the human SCN3A of Clare et al. (*supra*), and that of Jeong et al. (*supra*)

Figure 8 shows the amino acid alignment of the hNaIII18 of the present invention, with that of the human SCN3A of Clare et al. (*supra*), and that of Jeong et al. (*supra*)

Figure 9A-D shows results of electrophysiology of hNaIII18-transfected HEK293 cells. Figure 9A demonstrates the activation threshold voltage; Figure 9B, the steady state V ½ inactivation voltage; Figure 9C, the recovery time after inactivation; and Figure 9D, the inactivation kinetics.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is based, in part, on the discovery of a splice variant of the human NaIII channel α subunit. The human NaIII α subunit isoform, designated herein as "hNaIII18", was cloned by RT-PCR from human embryonic

brain total RNA (Clontech, Palo Alto, CA), using human NaIII specific primers. Primers were designed from a sequence identified by searching the NCBI Human Genome database, using the human NaIII mRNA sequence (GenBank accession no. AJ251507) using reverse-transcriptase PCR (RT-PCR). PCR fragments were cloned into the mammalian expression vector and the complete DNA sequence was determined.

The hNaIII18 sequence of the invention contains an additional 147 nucleotides that do not appear in the human NaIII cDNA mentioned above (SEQ ID NO: 3). Splicing in this region (nucleotides +9 to +96) had been described for the rat NaIII sodium channel, but not for the human NaIII channel when this work was initiated. The nucleotide sequence of Jeong et al. 2000, *supra*, also containing the 147 nucleotide insert and encoding an amino acid sequence similar to that of SEQ ID NO: 2, was deposited in GenBank (Accession No. AF225987, SEQ ID NO: 5), and is described in International PCT publication WO 01/96552 (in Japanese). The novel sequence (SEQ ID NO: 1) presented herein differs from that of SEQ ID NO:5 by 37 nucleotides out of 6093 aligned. None of the differences are found within the 147-nucleotide insertion. The amino acid sequence presented herein in SEQ ID NO: 2, differs from the SEQ ID NO:5 amino acid sequence by 12 amino acids out of 2000, with none of the differences being found in the region containing the 49 amino acid insert.

Transient transfection of the novel splice variant of the invention (SEQ ID NO: 1) results in expression of functional sodium channels in mammalian cells (cell line HEK293). Stable transfection and expression of the hNaIII18 also was achieved in HEK293 cells.

Protein expression was confirmed in the stably transfected HEK293 cells by immunocytochemistry and Western blotting. A protein having a size of about 220 kD protein, corresponding to the expected molecular weight of hNaIII18 was identified. Functional hNaIII18 activity was confirmed by electrophysiology.

Thus, the present invention advantageously provides hNaIII18 protein, including fragments and derivatives thereof; hNaIII18-encoding nucleic acids, and portions thereof including oligonucleotide primers and probes surrounding and within the region containing the 147 nucleotide insert, and hNaIII18 regulatory sequences;

hNaIII18-specific antibodies; and related methods of using these materials to detect the presence of hNaIII18 proteins or nucleic acids.

The present invention also provides an assay method for screening to identify selective modulators of hNaIII18-containing sodium ion channel activity. The method involves detecting whether a test compound increases or decreases the activity of the sodium channel, as determined, *e.g.*, by measuring current phase (electrophysiology) and ion selectivity. The assay method is preferably conducted using at least one host cell that expresses or overexpresses a functional sodium channel comprising hNaIII18, or a membrane preparation prepared therefrom. In one embodiment, the test compound inhibits (antagonizes) the activity of the sodium channel. In another embodiment, the test compound potentiates (agonizes) the activity of the sodium channel. The test system preferably involves the use of an appropriate cell culture medium to permit cell growth and viability, as well as tissue culture plates or arrays containing the host cells in the cell culture medium. In specific embodiments, host cells are mammalian cell lines such as, *e.g.*, the HEK293 cell line, although appropriate cells from other organisms, such as, *e.g.*, *Xenopus* cells, can alternatively be utilized.

The specification and figures include the following nucleotide or amino acid sequences: hNaIII18 polynucleotide (SEQ ID NO:1); hNaIII18 amino acid sequence (SEQ ID NO:2); SCN3A nucleotide sequence (SEQ ID NO:3; Clare et al., *supra*; GenBank AJ251507); SCN3A amino acid sequence (SEQ ID NO:4; Clare et al., *supra*; GenBank AJ201507); SCN3A splice variant nucleotide sequence (SEQ ID NO:5; Jeong et al., *supra*; GenBank AF225987); SCN3A splice variant amino acid sequence (SEQ ID NO:6; Jeong et al., *supra*; GenBank AF225987); forward primer utilized in Example 1 (SEQ ID NO:7); and reverse primer utilized in Example 1 (SEQ ID NO:8).

General Definitions

The following definitions are provided for clarity and illustrative purposes only, and are not intended to limit the scope of the invention.

As used herein, the term "isolated" means that the referenced material is removed from the environment in which it is normally found. Thus, an isolated

biological material can be free of cellular components, *i.e.*, components of the cells in which the material is found or produced in nature. In the case of nucleic acid molecules, an isolated nucleic acid includes a PCR product, an mRNA, a cDNA, or a restriction fragment. In another embodiment, an isolated nucleic acid is preferably excised from the chromosome in which it may be found, and more preferably is no longer joined to non-regulatory, non-coding regions, or to other genes, located upstream or downstream of the gene contained by the isolated nucleic acid molecule when found in the chromosome. In yet another embodiment, the isolated nucleic acid lacks one or more naturally occurring introns. Isolated nucleic acid molecules include sequences inserted into plasmids, cosmids, artificial chromosomes, phages and the like. Thus, in a specific embodiment, a recombinant nucleic acid is an isolated nucleic acid. An isolated protein may be associated with other proteins or nucleic acids, or both, with which it associates in the cell, or with cellular membranes if it is a membrane-associated protein. A protein expressed from a vector in a cell, particularly a cell in which the protein is normally not expressed, is also a regarded as isolated. An isolated organelle, cell, or tissue is removed from the anatomical site in which it is found in a cell or an organism. An isolated material may be, but need not be, purified. As used herein to refer to nucleic acids, the term "isolated" does not encompass man-made genomic or cDNA libraries.

The term "purified" as used herein refers to material that has been isolated under conditions that reduce or eliminate the presence of unrelated materials, *i.e.*, contaminants, including native materials from which the material is obtained. For example, a purified protein is preferably substantially free of other proteins or nucleic acids with which it is associated in a cell; a purified nucleic acid molecule is preferably substantially free of proteins or other unrelated nucleic acid molecules with which it can be found within a cell. As used herein, the term "substantially free" is used operationally, in the context of analytical testing of the material. Preferably, purified material substantially free of contaminants. Purity can be evaluated by chromatography, gel electrophoresis, immunoassay, composition analysis, biological assay, and other methods known in the art.

Methods for purification are well-known in the art. For example, nucleic acids can be purified by precipitation, chromatography (including preparative

solid phase chromatography, oligonucleotide hybridization, and triple helix chromatography), ultracentrifugation, and other means. Polypeptides and proteins can be purified by various methods including, without limitation, preparative disc-gel electrophoresis, isoelectric focusing, HPLC, reversed-phase HPLC, gel filtration, ion exchange and partition chromatography, precipitation and salting-out chromatography, extraction, and countercurrent distribution. For some purposes, it is preferable to produce the protein in a recombinant system so that it contains an additional sequence tag that facilitates purification, such as, but not limited to, a polyhistidine sequence (His®-tag; Novagen, Madison, WI), or a sequence that specifically binds to an antibody, such as the FLAG® tag (Sigma, St. Louis, MO), HA-tag (Roche Diagnostics, Indianapolis, IN), or that can be column-purified such as via the use of glutathione-S-transferase (GST). The polypeptide can then be purified from a crude lysate of the host cell by chromatography on an appropriate solid-phase matrix. Alternatively, antibodies produced against the protein or against peptides derived therefrom can be used as purification reagents. Cells can be purified by various techniques, including centrifugation, matrix separation (*e.g.*, nylon wool separation), panning and other immunoselection techniques, depletion (*e.g.*, complement depletion of contaminating cells), and cell sorting (*e.g.*, fluorescence activated cell sorting (FACS)). Other purification methods are possible. A purified material may contain less than about 50%, preferably less than about 75%, and most preferably less than about 90%, by weight of the cellular components with which it was originally associated. The "substantially pure" indicates the highest degree of purity that can be achieved using conventional purification techniques known in the art.

In a specific embodiment, the term "about" or "approximately" means plus or minus 10% of the stated numerical value or range.

As use herein, the term "ion channel" refers to a transmembrane pore that presents a hydrophilic channel for ions to cross a lipid bilayer down their electrochemical gradients. In a preferred embodiment, the ion channel is a voltage-gated sodium ion channel. A "sodium channel" is an ion channel that is selective for sodium ions.

A "sample" as used herein refers to a biological material that can be obtained and tested for the presence or expression of: (i) an hNaIII18 subunit-containing ion channel; or (ii) an hNaIII18 subunit protein; or (iii) an hNaIII18 subunit-encoding nucleic acid. Such samples can be obtained from animal, preferably mammalian, and more preferably human subjects, and include tissue samples, especially CNS or PNS tissues, as well as cell cultures derived from such tissues. Alternatively, such samples can comprise cells genetically engineered to express or overexpress an hNaIII18 subunit-containing ion channel or an hNaIII18 subunit protein. Such cells are preferably eukaryotic, but may alternatively be prokaryotic cells. Eukaryotic cells are preferably mammalian cells, but may alternatively be *Xenopus* cells.

Non-human animals include, without limitation, laboratory animals such as mice, rats, rabbits, hamsters, guinea pigs, etc.; domestic animals such as dogs and cats; and farm animals such as sheep, goats, pigs, horses, and cows.

The term "modulator" refers to a compound that binds to an ion channel comprising the hNaIII18 subunit protein of the invention and differentially affects the activity of the ion channel in response to a stimulus that normally activates the function of that ion channel when compared to the activity of the ion channel not contacted with the compound. Ion channel activity can be measured, *e.g.*, using electrophysiological techniques, or according to other known methods in the art. In a preferred embodiment, the ion channel is a sodium channel.

The terms "inhibitor" and antagonist refer to a compound that binds to the ion channel comprising hNaIII18, and blocks, inhibits, impedes or reduces the activity of that ion channel.

An "agonist" is defined as a compound that binds to the ion channel comprising hNaIII18, and promotes, enhances, stimulates or potentiates the normal biological function of the sodium channel. A "partial agonist" binds as to the ion channel or a subunit thereof, as does a full agonist, but promotes only partial function.

As used herein the term "transfected cell" or "transformed cell" refers to a host cell that has been genetically engineered to express or overexpress a nucleic acid encoding a hNaIII18 subunit, preferably in combination with one or more β subunits such as, *e.g.*, β-subunits 1-3 as described in GenBank Accession Nos.

U87445, AF007783, AH005825, AF007783, AF04948, L10338 and L16242, among others. Any cell can be used, preferably a eukaryotic cell, and more preferably a vertebrate cells, preferably a mammalian cell, or a *Xenopus* cell. Such cells additionally can be genetically engineered to coexpress or overexpress a different sodium channel subunit. Such genetically engineered cells include those cells into which one or more heterologous hNaIII18-encoding nucleic acids have been introduced and are expressed or overexpressed. Such genetically engineered cells also include those cells engineered to express or overexpress one or more endogenous hNaIII18 subunits, for example, by gene activation technology.

Such cells are particularly suitable to conduct an assay to screen for compounds that modulate the function of the hNaIII18 subunit-containing sodium channel in response to an appropriate stimulus (*e.g.*, TTX). An "assay method" typically makes use of one or more such cells, *e.g.*, in a microwell plate or some other culture system. The effects of a test compound can be determined on a single cell or on a collection of cells sufficient to allow measurement of ionic current, activation threshold, or ionic permeability characteristics of the hNaIII18 subunit-containing sodium channels. For example, single cells can be tested, *e.g.*, by use of patch clamp or other appropriate electrophysiological techniques.

A "test compound" or "candidate compound" is any molecule that can be tested for its ability to bind to the hNaIII18 subunit-containing sodium channel,or to a subunit thereof, and preferably modulate on the activity of the hNaIII18 subunit-containing sodium channel. A compound that binds and modulates a hNaIII18 subunit-containing sodium channel is a "lead compound" suitable for further testing and development.

The term "ligand" can alternatively be used to refer to any compound or peptide or polypeptide that binds to and modulates the activity of a hNaIII18 subunit, or a sodium channel comprising hNAIII18.

The term "pain disorder" includes chronic pain, defined as pain lasting longer than one month (Bonica, Semin Anesth 1986, 5:82-99), and is characterized by unrelenting persistent pain that is not amenable to routine pain control methods. The term "pain disorder" also includes neuropathic pain and nociceptive pain.

"Chronic pain" can be defined as pain lasting longer than one month (Bonica, Semin Anesth 1986, 5:82-99), and is characterized by unrelenting persistent pain that is not amenable to routine pain control methods. Chronic pain includes, but is not limited to, inflammatory pain, postoperative pain, cancer pain, osteoarthritis pain associated with metastatic cancer, trigeminal neuralgia, acute herpetic and postherpetic neuralgia, diabethic neuropathy, causalgia, brachial plexus avulsion, occipital neuralgia, reflex sympathetic dystrophy, fibromyalgia, gout, phantom limb pain, burn pain, pain associated with spinal cord injury, multiple sclerosis, reflex sympathetic dystrophy and lower back pain and other forms of neuralgia, neuropathic, and idiopathic pain syndromes.

"Neuropathic pain" can be caused by injury or infection of peripheral sensory nerves. It includes, but is not limited to pain from peripheral nerve trauma, herpes virus infection, diabetes mellitus, causalgia, plexus avulsion, neuroma, limb amputation, and vasculitis. Neuropathic pain is also caused by nerve damage from chronic alcoholism, human immunodeficiency virus infection, hypothyroidism, uremia, or vitamin deficiences. Neuropathic pain includes but is not limited to pain caused by nerve injury such as, for example, the pain from which diabetics suffer.

Chronic and neuropathic types of pain generally arises from injury to the peripheral or central nervous tissue.

"Nociceptive pain" is due to activation of pain-sensitive nerve fibers, either somatic or visceral. Nociceptive pain generally results as a response to direct tissue damage. The initial trauma causes the release of several chemicals including bradykinin, serotonin, substance P, histamine, and prostaglandin. When somatic nerves are involved, the pain is typically experienced as aching or pressure-like.

Molecular Biology Definitions

In accordance with the present invention there may be employed conventional molecular biology, microbiology, and recombinant DNA techniques within the skill of the art. See, *e.g.*, Sambrook, Fritsch & Maniatis, Molecular Cloning: A Laboratory Manual, Second Edition (1989) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York (herein "Sambrook et al., 1989"); DNA Cloning: A Practical Approach, Volumes I and II (D.N. Glover ed. 1985);

Oligonucleotide Synthesis (M.J. Gait ed. 1984); Nucleic Acid Hybridization [B.D. Hames & S.J. Higgins eds. (1985)]; Transcription And Translation [B.D. Hames & S.J. Higgins, eds. (1984)]; Animal Cell Culture [R.I. Freshney, ed. (1986)]; Immobilized Cells And Enzymes [IRL Press, (1986)]; B.Perbal, A Practical Guide To Molecular Cloning (1984); F.M. Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, Inc. (1994).

"Amplification" of DNA as used herein denotes the use of exponential amplification, techniques such as polymerase chain reaction (PCR), and non-exponential amplification, such as linked linear amplification, to increase the concentration of a particular DNA sequence within a mixture of DNA sequences. For a description of PCR see Saiki et al., Science 1988, 239:487. For a description of linked linear amplification, see U.S. Patent Nos. 6,335,184 and 6,027,923 and Reyes et al. Clinical Chemistry 2001; 47: 131-40; Wu et al. Genomics 1989; 4: 560-569.

As used herein, "sequence-specific oligonucleotides" refers to related sets of oligonucleotides that can be used to detect allelic variations or mutations in the hNaIII18 gene, or can be used for amplification of an hNAIII18 encoding-nucleic acid.

The nucleic acid molecules (polynucleotides) described herein may be flanked by natural regulatory (expression control) sequences, or may be associated with heterologous sequences, including promoters, internal ribosome entry sites (IRES) and other ribosome binding site sequences, enhancers, response elements, suppressors, signal sequences, polyadenylation sequences, introns, 5'- and 3'- non-coding regions, and the like. The nucleic acid molecules may also be modified by many means known in the art. Non-limiting examples of such modifications include methylation, "caps", substitution of one or more of the naturally occurring nucleotides with an analog, and internucleotide modifications such as, for example, replacement with uncharged linkages (*e.g.*, methyl phosphonates, phosphotriesters, phosphoroamidates, carbamates, etc.) and with charged linkages (*e.g.*, phosphorothioates, phosphorodithioates, etc.). Polynucleotides may contain one or more additional covalently linked moieties, such as, for example, proteins (*e.g.*, nucleases, toxins, antibodies, signal peptides, poly-L-lysine, etc.), intercalators (*e.g.*, acridine, psoralen, etc.), chelators (*e.g.*, metals, radioactive metals, iron, oxidative

metals, etc.), and alkylators. The polynucleotides may be derivatized by formation of a methyl or ethyl phosphotriester or an alkyl phosphoramidate linkage. Furthermore, the polynucleotides herein may also be modified with a label capable of providing a detectable signal, either directly or indirectly. Exemplary labels include radioisotopes, fluorescent molecules, biotin, and the like.

A "coding sequence" or a sequence "encoding" an expression product, such as an RNA, polypeptide, protein, or enzyme, is a nucleotide sequence that, when expressed, results in the production of that RNA or polypeptide, *i.e.,* the nucleotide sequence encodes an amino acid sequence for that polypeptide. A coding sequence or "open reading frame (ORF)" for a polypeptide will typically include a start codon (usually ATG) and a stop codon.

The term "gene", also called a "structural gene" refers to a basic unit of hereditary material. Specifically a gene is an ordered sequence of DNA nucleotide bases that encodes one polypeptide chain (via mRNA). The gene includes regions preceding and following the coding region (such as promoter sequences, a 5'-untranslated region, and a 3'-untranslated region, which affect, for example, the conditions under which the gene is expressed) as well as (in eukaryotes) intervening sequences (introns) between individual coding segments (exons).

A "promoter sequence" is a DNA regulatory region capable of binding RNA polymerase in a cell and initiating transcription of a downstream (3' direction) coding sequence. For purposes of defining the present invention, the promoter sequence is bounded at its 3' terminus by the transcription initiation site and extends upstream (5' direction) to include the minimum number of bases or elements necessary to initiate transcription at levels detectable above background. Within the promoter sequence will be found a transcription initiation site (conveniently defined for example, by mapping with nuclease S1), as well as protein binding domains (consensus sequences) responsible for the binding of RNA polymerase. The present invention includes the hNaIII18 gene promoter found in the genome, which can be operatively associated with a hNaIII18 coding sequence with a heterologous coding sequence.

The term "host cell" means any cell of any organism that is selected, modified, transformed, grown, or used or manipulated in any way, for the production

of a substance by the cell, for example, the expression by the cell of a gene, a DNA or RNA sequence, or a polypeptide. Host cells can further be used for screening or other assays, as described *infra*.

A coding sequence is "under the control of" or "operatively associated with" transcriptional and translational control sequences in a cell when such control sequences operate to effect RNA polymerase transcription of the coding sequence into mRNA, which is then trans-RNA spliced (if it contains introns) and translated, in the case of mRNA, into the protein encoded by the coding sequence.

The terms "express" and "expression" mean allowing or causing the information in a gene or cDNA or mRNA sequence to become manifest, for example, by producing a protein by activating the cellular functions involved in transcription and translation of a corresponding gene, cDNA or mRNA sequence. A gene or cDNA sequence is expressed in or by a cell to form an "expression product" such as a protein. The expression product itself, *e.g.,* the resulting protein, may also be said to be "expressed" by the cell. An expression product can be characterized as intracellular, extracellular, transmembrane, or secreted depending on the particular product. The hNaIII18 subunit protein of the invention is typically expressed as a transmembrane protein with intracellular and extracellular domains.

The term "transfection" means the introduction of a "foreign" (*i.e.*, extrinsic or extracellular) gene, DNA or RNA sequence into a host cell so that the host cell will express the introduced gene or sequence to produce a desired substance, typically a protein encoded by the introduced gene or sequence. The introduced gene or sequence may also be called a "cloned" or "foreign" or "heterologous" gene or sequence, and may include regulatory or control sequences, such as start, stop, promoter, signal, secretion, or other sequences used by a cell's genetic machinery. The gene or sequence may include non-functional sequences or sequences with no known function.

The term "transformation" refers to the process by which DNA is introduced from the surrounding medium into a prokaryotic host cell.

The term "transduction" refers to the introduction of DNA into a prokaryotic host cell via a bacterial virus, or bacteriophage.

A prokaryotic or eukaryotic host cell that receives and expresses introduced DNA or RNA has been "transformed" and is a "transformant" or a "clone." The DNA or RNA introduced into a host cell can come from any source, including cells of the same genus or species as the host cell, or cells of a different genus or species, or synthetic sequences.

The transformed cells of the invention are particularly suitable for an assay system for the detection of compounds that modulate the function of hNaIII18 subunit-containing sodium channels in response to activation, *e.g.*, in response to exposure TTX. An "assay method" makes use of one or more such cells, *e.g.*, in a microwell plate or some other culture or assay system to permit evaluation of the effects of a test compound on the cell(s), *e.g.*, by measuring ionic current or activation threshold characteristics of the hNaIII18 subunit-containing sodium channel.

The term "recombinantly engineered cell" refers to any prokaryotic or eukaryotic cell that has been manipulated to express or overexpress the hNaIII18 subunit by any appropriate method, including transfection, transformation or transduction. This term also includes endogenous activation of a hNaIII18 gene in a cell that does not normally express hNaIII18 or that expresses the protein at a sub-optimal level.

The terms "vector", "cloning vector" and "expression vector" mean the vehicle by which a DNA or RNA sequence (*e.g.*, a foreign gene) can be introduced into a host cell, so as to transform the host and promote expression (*e.g.*, transcription and translation) of the introduced sequence. Vectors include plasmids, cosmids, phages, viruses, etc.; they are discussed in greater detail below.

Vectors typically comprise the DNA of a transmissible agent, into which foreign DNA is inserted. A common way to insert one segment of DNA into another segment of DNA involves the use of restriction enzymes to cleave DNA at specific restriction sites. A "cassette" refers to a DNA coding sequence or segment of DNA that codes for an expression product that can be inserted into a vector at defined restriction sites. The cassette restriction sites are designed to ensure insertion of the cassette in the proper reading frame. Generally, foreign DNA is inserted at one or more restriction sites of the vector DNA, and then is carried by the vector into a host cell along with the transmissible vector DNA. A segment or sequence of DNA

having inserted or added DNA, such as an expression vector, can also be called a "DNA construct." A common type of vector is a plasmid. A plasmid vector often contains coding DNA and promoter DNA and has one or more restriction sites suitable for inserting foreign DNA. Coding DNA is a DNA sequence that encodes a particular amino acid sequence for a particular protein. Promoter DNA is a DNA sequence that initiates, regulates, or otherwise mediates or controls the expression of the coding DNA. Promoter DNA and coding DNA may be from the same gene or from different genes, and may be from the same or different organisms. A large number of vectors, including plasmid and fungal vectors, have been described for replication and/or expression in a variety of eukaryotic and prokaryotic hosts. Non-limiting examples include pKK plasmids (Clonetech), pUC plasmids, pET plasmids (Novagen, Inc., Madison, WI), pRSET or pREP plasmids (Invitrogen, San Diego, CA), or pMAL plasmids (New England Biolabs, Beverly, MA), and many appropriate host cells. Recombinant cloning vectors will often include one or more replication systems for cloning or expression, one or more markers for selection in the host, *e.g.*, antibiotic resistance, and one or more expression cassettes.

The term "expression system" means a host cell and compatible vector under suitable conditions, *e.g.*, for the expression of a protein coded for by foreign DNA carried by the vector and introduced to the host cell. Common expression systems include *E. coli* host cells and plasmid vectors, insect host cells and baculovirus vectors, and mammalian host cells and vectors.

The term "heterologous" refers to a combination of elements not naturally occurring. For example, heterologous DNA refers to DNA not naturally present in that cell. Alternativley, heterologous DNA refers to combinations of sequences that do not naturally occur together in that cell, *e.g.*, promoter sequences from a gene from one cell type linked to coding sequences of a gene that is not normally controlled by that promoter or expressed by another cell type. Preferably, the heterologous DNA includes a gene foreign to the cell. A heterologous expression regulatory element is such an element operatively associated with a different gene than the one it is operatively associated with in nature. In the context of the present invention, a hNaIII18 gene is heterologous to the vector DNA in which it is inserted

for cloning or expression purposes, and is heterologous to a host cell containing such a vector in which it is expressed, *e.g.*, a HEK cell.

The terms "mutant" and "mutation" mean any detectable change in genetic material, *e.g.*, DNA, or any process, mechanism, or result of such a change. This includes gene mutations in which the structure (*e.g.*, DNA sequence) of a gene is altered; any gene or DNA arising from any mutation process; and any expression product (*e.g.*, protein or enzyme) expressed by a non-silent modification of a gene or DNA sequence. The term "variant" may also be used to indicate a modified or altered gene, DNA sequence, polypeptide, cell, etc., *i.e.*, any kind of mutant therefrom.

"Sequence-conservative variants" or "degenerate variants" of a polynucleotide sequence are those in which a change of one or more nucleotides in a given codon position results in no alteration in the amino acid encoded at that position.

"Function-conservative variants" are those in which a given amino acid residue in a protein has been changed without substantially altering the function of the polypeptide, including, but not limited to, replacement of an amino acid with a residue having similar properties (such as, for example, polarity, hydrogen bonding potential, acidic, basic, hydrophobic, aromatic, and the like). Amino acids with similar properties are well known in the art. For example, arginine, histidine and lysine are hydrophilic-basic amino acids and may be interchangeable. Similarly, isoleucine, a hydrophobic amino acid, may be replaced with leucine, methionine or valine. Such changes are expected to have little or no effect on the apparent molecular weight, isoelectric point, or function of the protein. Amino acid residues may be varied in a protein so that the percent amino acid sequence identity between the original protein and the variant may be, for example, at least 70%, 80%, 90%, 95% or 99%, as determined according to a default alignment scheme such as by the Cluster Method, wherein similarity is based on the MEGALIGN algorithm, or BLAST. A "function-conservative variant" of the present invention includes those polypeptides having the above-described amino acid sequence identities , and having the same or substantially similar functions as the native or parent hNaIII18 subunit protein of the invention

As used herein, the term "homologous" refers to the relationship between proteins that possess a "common evolutionary origin," including proteins

from superfamilies (*e.g.*, the immunoglobulin superfamily) and homologous proteins from different species (*e.g.*, myosin light chain, etc.) (Reeck et al., Cell 1987, 50:667). Such proteins (and their encoding genes) have sequence homology, as reflected by their sequence similarity or sequence identity, whether in terms of percent similarity or the presence of specific residues or motifs at conserved positions.

Accordingly, the term "sequence similarity" or "sequence identity" refers to the degree of identity or correspondence between nucleic acid or amino acid sequences of proteins that may or may not share a common evolutionary origin (see Reeck et al., *supra*). However, in common usage and in the instant application, the term "homologous," when modified with an adverb such as "highly," may refer to sequence similarity and may or may not relate to a common evolutionary origin.

In a specific embodiment, two DNA sequences are "substantially homologous" or "substantially similar" when at least about 80%, and most preferably at least about 90, 95% or 99% of the nucleotides match over the defined length of the DNA sequences, as determined by sequence comparison algorithms, such as BLAST, FASTA, DNA Strider, etc. An example of such a sequence is an allelic or species variant of the specific hNaIII18 gene of the invention. Sequences that are substantially homologous can be identified by comparing the sequences using standard software available in sequence data banks, or in a Southern hybridization experiment under, for example, stringent conditions as defined for that particular system.

Similarly, in a particular embodiment, two amino acid sequences are "substantially homologous" or "substantially similar" when greater than 80%, 90%, 95% or 99% of the amino acids are identical. Preferably, the similar or homologous sequences are identified by alignment using, for example, the GCG (Genetics Computer Group, Program Manual for the GCG Package, Version 7, Madison, Wisconsin) pileup program, or any of the programs described above (BLAST, FASTA, etc.).

A nucleic acid molecule is "hybridizable" to another nucleic acid molecule, such as a cDNA, genomic DNA, or RNA, when a single stranded form of the nucleic acid molecule can anneal to the other nucleic acid molecule or its complement under the appropriate conditions of temperature and solution ionic

strength (see Sambrook *et al.*, *supra*). The conditions of temperature and ionic strength determine the "stringency" of the hybridization. For preliminary screening for homologous nucleic acids, low stringency hybridization conditions, using a Tm (melting temperature) in the range of about 55°C with low salt and/or denaturant concentrations, can be used, *e.g.,* 5x SSC, 0.1% SDS, 0.25% milk, and no formamide; or 30% formamide, 5x SSC, 0.5% SDS. Moderate stringency hybridization conditions correspond to use of a higher Tm, and higher concentrations of salt and/or denaturants, *e.g.,* 40% formamide, with 5x or 6x SSC. High stringency hybridization conditions correspond to the highest Tm and concentrations of salt/and/or denaturants, *e.g.*, 68°C, 50% formamide, 5x or 6x SSC. SSC is a 0.15M NaCl, 0.015M Na-citrate buffer. Hybridization requires that the two nucleic acids contain complementary sequences, although depending on the stringency of the hybridization, mismatches between bases are possible. The appropriate stringency for hybridizing nucleic acids depends on the length of the nucleic acids and the degree of complementation, as known in the art. The greater the degree of similarity or homology between two nucleotide sequences, the higher the value of Tm for hybrids of nucleic acids having those sequences. The relative stability (corresponding to higher Tm) of nucleic acid hybridizations decreases in the following order: RNA:RNA, DNA:RNA, DNA:DNA. For hybrids of greater than 100 nucleotides in length, equations for calculating Tm have been derived (see Sambrook *et al.* 1989, *supra*, 9.50-9.51). For hybridization with shorter nucleic acids, *i.e.,* oligonucleotides, the position of mismatches becomes more important, and the length of the oligonucleotide determines its specificity (see Sambrook *et al.*, *supra*, 11.7-11.8). A minimum length for a hybridizable nucleic acid is at least about 10 nucleotides; preferably at least about 15 nucleotides; and more preferably at least about 20 nucleotides.

In a specific embodiment, the term "standard hybridization conditions" refers to a Tm of 55°C, and utilizes conditions as set forth above. In a preferred embodiment, the Tm is about 60°C; in a more preferred embodiment, the Tm is about 65°C. In a specific embodiment, "high stringency" refers to hybridization and/or washing conditions at 68°C, in 0.2 x SSC, at 42°C in 50% formamide, 4x SSC, or under conditions that afford levels of hybridization equivalent to those observed under either of these two conditions.

As used herein, the term "oligonucleotide" refers to a nucleic acid, generally of at least 10, preferably at least 15, and more preferably at least 20 nucleotides, preferably no more than 100 nucleotides, that is hybridizable to a genomic DNA molecule, a cDNA molecule, or an mRNA molecule, or other nucleic acid of interest. Oligonucleotides can be labeled, *e.g.*, with γ^{32}P-nucleotides or nucleotides to which a label, such as biotin, has been covalently conjugated. In one embodiment, a labeled oligonucleotide can be used as a probe to detect the presence of a nucleic acid. In another embodiment, oligonucleotides (one or both of which may be labeled) can be used as PCR primers, either for cloning a full length nucleic acid or a fragment of a nucleic acid encoding the hNaIII18 subunit, or to detect the presence of nucleic acids encoding hNaIII18. In a further embodiment, an oligonucleotide of the invention can form a triple helix with a hNaIII18-encoding DNA molecule. Generally, oligonucleotides are prepared synthetically, preferably on a nucleic acid synthesizer. Accordingly, oligonucleotides can be prepared with non-naturally occurring phosphoester analog bonds, such as thioester bonds, etc.

The present invention also provides antisense nucleic acids, which may be used to inhibit expression of the hNaIII18 subunit protein of the invention. Inhibition of hNaIII18 expression may be desired when upregulation of hNaIII18 expression or excessive activation of an hNaIII18-containing ion channel induces or otherwise contributes to an increase in pain or a pain disorder in a subject.

An "antisense nucleic acid" is a single stranded nucleic acid molecule, which may be DNA, RNA, a DNA-RNA chimera, or derivatives thereof, which, on hybridizing under cytoplasmic conditions with complementary bases in an RNA or DNA molecule, inhibits the expression or translation of the encoded gene. If the RNA is an mRNA transcript, the antisense nucleic acid is a counter-transcript or mRNA-interfering complementary nucleic acid. As presently used, "antisense" broadly includes RNA-RNA interactions, RNA-DNA interactions, and RNase-H mediated arrest. Antisense nucleic acid molecules can be encoded by a recombinant gene for expression in a cell (e.g., U.S. Patent No. 5,814,500; U.S. Patent No. 5,811,234), or alternatively they can be prepared synthetically (see, e.g., U.S. Patent No. 5,780,607).

In addition to antisense sequences, the present invention also provides ribozymes useful to inhibit hNaIII18 expression. Ribozyme technology is described further in Intracellular Ribozyme Applications: Principals and Protocols, Ed. Rossi and Couture, 1999, Horizon Scientific Press

hNaIII18 Nucleic Acids

A polynucleotide molecule encoding hNaIII18, whether genomic DNA or cDNA, can be isolated from any source, particularly from a human cDNA or genomic library. Methods for obtaining specific polynucleotide molecules gene are well known in the art, as described above (see, *e.g.,* Sambrook *et al.*, 1989, *supra*). The DNA may be obtained by standard procedures known in the art from cloned DNA (*e.g.,* a DNA "library"), and preferably is obtained from a cDNA library prepared from tissues with high level expression of the encoded protein, by chemical synthesis, by cDNA cloning, or by the cloning of genomic DNA, or fragments thereof, purified from the desired cell (See, for example, Sambrook *et al.*, 1989, *supra*; Glover, D.M. (ed.), 1985, DNA Cloning: A Practical Approach, MRL Press, Ltd., Oxford, U.K. Vol. I, II). Clones derived from genomic DNA may contain regulatory and intron DNA regions in addition to coding regions. Clones derived from cDNA will not contain intron sequences. Whatever the source, the polynucleotide molecule should be cloned into a vector suitable for its propagation. Identification of a specific DNA fragment containing the desired hNaIII18-encoding sequence may be accomplished in a number of ways. For example, a portion of a hNaIII18 encoding polynucleotide molecule exemplified *infra* can be purified and labeled to prepare a labeled probe, and the generated DNA library may be screened by nucleic acid hybridization to the labeled probe (Benton and Davis, Science 1977, 196:180; Grunstein and Hogness, Proc. Natl. Acad. Sci. U.S.A. 1975, 72:3961). Those DNA fragments with substantial homology to the probe, such as an allelic variant from another individual, will hybridize. In a specific embodiment, highest stringency hybridization conditions are used to identify a homologous hNaIII18 gene.

Further selection can be carried out on the basis of the properties of the gene, *e.g.,* if the gene encodes a protein product having the same physicochemical profile (*i.e.*, isoelectric, electrophoretic, electrophysiological, amino acid composition,

partial or complete amino acid sequence, antibody binding activity, or ligand binding profile) of the hNaIII18 subunit protein disclosed herein. Thus, the presence of the nucleic acid may be detected by assays based on the physical, chemical, immunological, or functional properties of its expressed product.

Other DNA sequences which encode substantially the same amino acid sequence as a hNaIII18 gene may be used in the practice of the present invention. These include but are not limited to allelic variants, species variants, sequence conservative variants, and function conservative variants.

Amino acid substitutions may also be introduced to substitute an amino acid with a particularly preferable property. For example, a Cys may be introduced at a potential site for disulfide bridges with another Cys.

Polynucleotide molecules encoding the hNaIII18 subunit , and the encodied polypeptide, derivatives and analogs thereof ,can be produced by various methods known in the art. The manipulations which result in their production can occur at the gene or protein level. For example, the cloned hNaIII18 gene or cDNA sequence can be modified by any of numerous strategies known in the art (Sambrook *et al.*, 1989, *supra*). The sequence can be cleaved at appropriate sites with restriction endonuclease(s), followed by further enzymatic modification if desired, isolated, and ligated *in vitro*. In the production of the polynucleotide molecule encoding a derivative or analog of hNaIII18, care should be taken to ensure that the modified polynucleotide sequence remains within the same translational reading frame as the hNaIII18 gene, uninterrupted by premature translational stop signals.

Additionally, the encoding nucleic acid sequence can be mutated *in vitro* or *in vivo* to create and/or destroy translation, initiation, and/or termination sequences, or to create variations in coding regions and/or form new restriction endonuclease sites or destroy preexisting ones, to facilitate further *in vitro* modification. Such modifications can be made to introduce restriction sites and facilitate cloning the polynucleotide molecule into an expression vector. Any technique for mutagenesis known in the art can be used, including but not limited to, *in vitro* site-directed mutagenesis (Hutchinson, C., *et al.*, J. Biol. Chem.1978; 253:6551; Zoller and Smith, DNA 1984; 3:479-488; Oliphant *et al.*, Gene 1986; 44:177; Hutchinson *et al.*, Proc. Natl. Acad. Sci. U.S.A.1986; 83:710), use of TAB

linkers (Pharmacia), etc. PCR techniques are preferred for site directed mutagenesis (see Higuchi, 1989, "Using PCR to Engineer DNA", in PCR Technology: Principles and Applications for DNA Amplification, H. Erlich, ed., Stockton Press, Chapter 6, pp. 61-70).

The identified and isolated polynucleotide molecule can then be inserted into an appropriate cloning vector. A large number of vector-host systems known in the art may be used. Possible vectors include, but are not limited to, plasmids or modified viruses, but the vector system must be compatible with the host cell used. Examples of vectors include, but are not limited to, *E. coli*, bacteriophages such as lambda derivatives, or plasmids such as Bluescript, pBR322 derivatives or pUC plasmid derivatives, *e.g.*, pGEX vectors, pmal-c, pFLAG, etc. The insertion into a cloning vector can, for example, be accomplished by ligating the DNA fragment into a cloning vector that has complementary cohesive termini. However, if the complementary restriction sites used to fragment the DNA are not present in the cloning vector, the ends of the DNA molecules may be enzymatically modified. Alternatively, any restriction site desired may be produced by ligating nucleotide sequences (linkers) onto the DNA termini; these ligated linkers may comprise specific chemically synthesized oligonucleotides encoding restriction endonuclease recognition sequences. In addition, simple PCR or overlapping PCR may be used to insert a fragment into a cloning vector.

Recombinant molecules can be introduced into host cells via transformation, transfection, infection, electroporation, etc., so that many copies of the gene sequence are generated. Preferably, the cloned gene is contained on a shuttle vector plasmid, which provides for propagation in a cloning cell, *e.g.*, *E. coli*, and facile purification for subsequent insertion into an appropriate expression cell line, if such is desired. For example, a shuttle vector, which is a vector that can replicate in more than one type of organism, can be prepared for replication in both *E. coli* and *Saccharomyces cerevisiae* by linking sequences from an *E. coli* plasmid with sequences from the yeast 2Φ plasmid.

In a preferred embodiment of the invention, the hNaIII18 sodium channel is cloned using a strategy designed to minimize mutations during cDNA

preparation, RT-PCR amplification, and growth in bacteria. This strategy is described in detail *infra*, in Example 1. The main points are summarized as follows:

First, as an alternative to conventional reverse transcriptases, which function optimally at temperatures of between 37 °C and 43 °C, this method employs an avian RNase (-) reverse transcriptase that functions optimally at temperatures between 50-65 °C. The higher temperature serves to decrease secondary structure of the RNA to produce higher cDNA yield.

Second, for amplification of the cDNA, an enzyme mixture comprising the conventional thermostable Taq polymerase and Pwo polymerase is used. This mixture is optimized to produce very large PCR products with low error frequency, thus decreasing the mutation frequency.

Third, the number of cycles of amplification is decreased to about 28, as opposed to the typical 30-35 cycles to further reduce the possibility of mutation.

Fourth, the PCR products are electrophoresed and visualized on an agarose gel containing Crystal Violet stain, as opposed to ethidium bromide. Crystal Violet allows visualization in white light, eliminating the need for UV exposure. UV is known to induce mutations in ethidium bromide-stained DNA.

Fifth, to minimize recombination and mutation in plasmid DNA during amplification in bacteria, the PCRamplified cDNA is cloned into a low-copy number expression vector that is engineered to have limited replication cycles and contains a tetracycline-resistance gene as a selectable marker instead of an ampicillinresistance gene. Fewer replication cycles again reduces the error rate during DNA synthesis, and selection with tetracycline is less likely to induce mutations in the plasmid than is ampicillin.

Sixth, competent bacterial cells that are designed to optimize cloning of unstable inserts are selected for the transformation, and grown at a lower temperature (30-33 °C versus 37 °C) to decrease the growth rate and therefore, minimize the possibility of mutations. In addition, the cultures should be maintained in exponential (log) phase throughout growth, eliminating the possibility of mutations resulting from starvation, poor aeration, and accumulation of toxic metabolites.

Seventh, small tetracycline resistant colonies are chosen for evaluation rather than large ones. Human NaIII expression during growth is expected to be toxic to bacteria, thus transformed cells will yield smaller colonies.

hNaIII18 Regulatory Nucleic Acids

Elements of the hNaIII18 promoter can be identified by scanning the human genomic region upstream of the hNaIII18 start site, *e.g.*, by creating deletion mutants and checking for expression, or by using an algorithm. Sequences up to about 6 kilobases (kb) or more upstream from the hNaIII18 start site can contain tissue-specific regulatory elements.

The term "hNaIII18 promoter" encompasses artificial or heterologous promoters. Such promoters can be prepared by deleting non-essential intervening sequences from the upstream region of the hNaIII18 promoter, or by joining upstream regulatory elements from the hNaIII18 promoter with a heterologous minimal promoter, such as the CMV immediate early promoter.

A hNaIII18 promoter can be operably associated with a heterologous coding sequence, *e.g.*, for a reporter gene (luciferase and green fluorescent proteins are examples of reporter genes) in a construct. This construct can be used to test for conditions or reagents that normally result in expression. This construct can be used in screening assays, described below, for hNaIII18 agonists and antagonists.

hNaIII18 regulatory nucleic acids of the present invention also include non-endogenous or artificial promoter sequences or sequences that encode zinc finger proteins that may be used, *e.g.*, in gene activation techniques, to initiate expression of hNaIII18 in cells where it is not normally expressed or to upregulate expression of the hNaIII18 subunit protein to a higher level where it would otherwise be expressed in suboptimal levels. Gene activation techniques that may be adapted to this use are described in the art, *e.g.*, in U.S. Patent Nos. 5,968,502 and 6,214,622 to Treco et al.

Expression of hNaIII18 Polypeptides

The primary goal for establishing a stable cell line expressing functional human sodium channels is to identify antagonists to inhibit sodium currents

mediated by the sodium channels. DRG neurons transmit nociceptive signals from the peripheral nervous system to the central nervous system. TTX-S and TTX-R sodium channels mediate the DRG action potentials responsible for these signals. However, DRG neurons express several different isoforms of TTX-S and TTX-R currents, thereby making it difficult to determine specific interactions of antagonists with particular subtypes of sodium channels in theses cells.

By generating a cell line that expresses a single sodium channel subtype, *e.g.*, hNaIII18, alone or preferably in combination with appropriate β subunits, the effect of drugs on the different sodium channel isoforms can be assessed. Previously, developing stable cell lines expressing nucleic acids containing repetitive sequences, such as those contained within sodium channel genes, has been challenging. In particular, cell lines expressing functional sodium channels have been difficult to generate due to the occurrence of inactivating mutations arising in the cDNA during the cloning process (*i.e.*, cDNA preparation, PCR amplification, and subsequent growth in bacteria). International PCT publication WO 98/38302 (Delgado et al.) describes isolation, cloning and expression of a rat TTX-S sodium channel in *Xenopus* oocytes. Experiments described therein demonstrate the formation of a functional TTX-S channel after injection of cRNA into *Xenopus* oocytes for the α-subunit, alone or in combination with the β1, β2 or β3 subunits. International PCT Publication WO 01/68681 (Aitken et al.) describes altered ion channel proteins having acquired sensitivity or refractory sensitivity to a gating agent. A rat sodium channel type II was modified by site-directed mutagenesis and PCR to contain sequences that bind α-scorpion toxins, which inactivate sodium channels, for use to evaluate ion channel activity and to screen for compounds for therapeutic applications. The modified sodium channel was then stably or transiently expressed in several mammalian host cells, including HEK293 variants and CHO cells, which were used in a high-throughput, plate-based screening assay.

International PCT publication WO/02068 (Korsgaard) describes stable cloning of a splice variant of a rat αI sodium channel in HEK293 cells.

To date, there have been no reports of stable expression of a cloned human sodium type III channel in mammalian cells. The method described herein combines several procedures to facilitate the cloning and generation of stable cell

lines containing such repetitive sequences, resulting in functional expression of such genes. In particular, the present invention describes the cloning and stable expression of a novel splice variant of human NaIII, designated hNaIII18.

The nucleotide sequence coding for hNaIII18, or an antigenic fragment, derivative or analog thereof, (including, *e.g.*, a chimeric protein) can be inserted into an appropriate expression vector, *i.e.*, a vector which contains the necessary elements for the transcription and translation of the inserted protein-coding sequence. Thus, a nucleic acid molecule having a nucleotide sequence encoding the hNaIII18 subunit protein of the invention can be operationally associated with a promoter in an expression vector of the invention. Either a cDNA or genomic sequence can be cloned and expressed under control of such regulatory sequences. Such vectors can be used to express functional, or functionally inactivated, hNaIII18 polypeptides.

The necessary transcriptional and translational signals can be provided on a recombinant expression vector, or they may be supplied from the native gene encoding hNaIII18 and/or its flanking regions.

Potential host-vector expression systems include but are not limited to mammalian cell systems transfected with expression plasmids or infected with virus (*e.g.*, vaccinia virus, adenovirus, adeno-associated virus, herpes virus, etc.); insect cell systems infected with virus (*e.g.*, baculovirus); microorganisms such as yeast containing yeast vectors; and bacteria transformed with bacteriophage, DNA, plasmid DNA, or cosmid DNA. The expression elements of vectors vary in their strengths and specificities. Depending on the host-vector system utilized, any one of a number of suitable transcription and translation elements may be used.

Expression of the hNaIII18 protein may be controlled by any promoter/enhancer element known in the art, but these regulatory elements must be functional in the host selected for expression. Promoters which may be used to control hNaIII18 gene expression include, but are not limited to, cytomegalovirus (CMV) promoter (see, *e.g.*, U.S. Patent Nos. 5,385,839 and 5,168,062), the SV40 early promoter region (Benoist and Chambon, Nature 1981; 290:304-310), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto, *et al.*, Cell, 1980; 22:787-797), the herpes thymidine kinase promoter (Wagner *et al.*,

Proc. Natl. Acad. Sci. U.S.A., 1981; 78:1441-1445), the regulatory sequences of the metallothionein gene (Brinster *et al.*, Nature, 1982; 296:39-42, prokaryotic expression vectors such as the β-lactamase promoter (Villa-Komaroff, *et al.*, Proc. Natl. Acad. Sci. U.S.A. 1978; 75:3727-3731), or the tac promoter (DeBoer, *et al.*, Proc. Natl. Acad. Sci. U.S.A. 1983; 80:21-25) (see also "Useful proteins from recombinant bacteria" in Scientific American, 1980, 242:74-94), promoter elements from yeast or other fungi such as the Gal 4 promoter, the ADC (alcohol dehydrogenase) promoter, PGK (phosphoglycerol kinase) promoter, alkaline phosphatase promoter, and transcriptional control regions that exhibit tissue specificity, such as, *e.g.*, endothelial cell-specific promoters.

Solubilized forms of the protein can be obtained where necessary by solubilizing inclusion bodies or reconstituting membrane components, *e.g.*, by treatment with detergent, and if desired sonication or other mechanical processes, as described above. The solubilized protein can be isolated using various techniques, such as polyacrylamide gel electrophoresis (PAGE), isoelectric focusing, 2-dimensional gel electrophoresis, chromatography (*e.g.*, ion exchange, affinity, immunoaffinity, and sizing column chromatography), centrifugation, differential solubility, immunoprecipitation, by any other standard technique for the purification of proteins, or by a combination of such techniques.

Since β-subunits 1-3 are known to bind the α-subunits of sodium channels, the present invention also contemplates co-expression of a β-subunit with NaIII18. While the role played by β-subunits in determining the pharmacological properties of voltage-gated sodium channels appears to be minor, at least for the commonly-studied binding sites,the β-subunits do appear to have effects on the biophysics (gating kinetics) of sodium channel function. Therefore, to the extent that biophysics and drug interactions are linked, the β-subunits may affect pharmacology of agents used to modulate sodium channel activity.Some known β-subunits that may be co-expressed with the NaIII18 subunit of the invention are described in Isom et al., Neuron 1994; 12:1183-94; International PCT publication WO 01/44293 to Plumpton et al.; International PCT publication WO 01/23570 to d'Andrea et al.; U.S. published patent application 2002/0045229 to Qin et al.; and under GenBank Accession Nos.

U87445, AF007783, AH005825, AF007783, AF04948, L10338 and L16242, among others

hNaIII18 Binding Partners

The present invention further provides a method for identifying physiological binding partners of hNaIII18. One method for evaluating and identifying hNaIII18 binding partners is the yeast two-hybrid screen. Preferably, the yeast two-hybrid screen is performed using an cell library with yeast that are transformed with recombinant hNaIII18. Alternatively, hNaIII18 can be used as a capture or affinity purification reagent. In another alternative, labeled hNaIII18 can be used as a probe for binding, *e.g.*, by immunoprecipitation or Western analysis. Several expected hNaIII18 binding partners are the sodium channel β subunits, as described in the section above.

Generally, binding interactions between hNaIII18 and any of its binding partners will be strongest under conditions approximating those found in the native cell, *i.e.*, physiological conditions of ionic strength, pH and temperature, and particularly those obtaining in the cell membrane. Perturbation of these conditions will tend to disrupt the stability of a binding interaction.

Antibodies to hNaIII18

Antibodies to hNaIII18 are useful, *inter alia*, for determining the presence of hNaIII18 in a cell and for cellular regulation (*i.e.*, inhibition) of hNaIII18 activity, as set forth below. According to the invention, a hNaIII18 polypeptide produced recombinantly or by chemical synthesis, and fragments or other derivatives or analogs thereof, including fusion proteins, may be used as immunogens to generate antibodies that recognize the hNaIII18 polypeptide. Such antibodies include but are not limited to polyclonal, monoclonal, chimeric, single chain, Fab fragments, and Fab expression libraries. Such an antibody binds specifically to hNaIII18, and may recognize either a mutant form of hNaIII18 or wild-type hNaIII18, or both. The antibodies of the present invention are specific for hNaIII18 and either do not recognize, or bind with lower affinity to, orthologs of hNaIII18. In one embodiment,

specific binding of such antibodies to hNaIII18 polypeptides provides the ability to detect the presence of the hNaIII18 polypeptide in a sample. In another embodiment, specific binding of such antibodies to hNaIII18 polypeptides provides the ability to preferentially inhibit the activity of hNaIII18, or an ion channel comprising hNaIII18.

Various procedures known in the art may be used for the production of antibodies against hNaIII18 polypeptides. These include but are not limited to the hybridoma technique originally developed by Kohler and Milstein (Nature 1975; 256:495-497), as well as the trioma technique, the human B-cell hybridoma technique (Kozbor *et al.*, Immunology Today 1983, 4:72; Cote *et al.*, Proc. Natl. Acad. Sci. 1983, 80:2026-2030), and the EBV-hybridoma technique to produce human monoclonal antibodies (Cole *et al.*, in Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, Inc., 1985, pp. 77-96).

hNaIII18 Agonists and Antagonists

The present invention also contemplates the identification of compounds that modulate hNaIII18 sodium channel activation and activity. Such compounds are useful, *e.g.*, for inhibiting (*i.e.*, antagonizing) or increasing (*i.e.*, agonizing) biological activities that are associated with sodium channel activation and/or as therapeutic agents for treating disorders associated with excessive sodium channel activation.

Compounds that modulate hNaIII18 activity or an activity associated therewith may be readily identified using screening methods of the present invention. In one embodiment, compounds identified by the screening methods of this invention bind to a hNaIII18-subunit containing ion channel. Compounds identified by the present method may antagonize or agonize hNaIII18 subunit-containing channel activity, as well as a related downstream biological effect (*e.g.*, the ability of DRG to transmit nociceptive signals from the PNS to the CNS) that are associated with excessive sodium channel current and activity.

In vivo or cell culture assays may be used to determine whether a test compound functions as an antagonist to inhibit hNaIII18 activity in cells. For instance, cell culture assays may be used to measure a test compound's ability to modulate an activity, such as induction, strength or duration of sodium channel

current associated with hNaIII18 subunit-containing sodium channel activity. Such assays generally comprise contacting a cell that expresses a hNaIII18 subunit containing sodium channel with a test compound. The cell should preferably be contacted with the test compound before or during exposure to an agent or stimulus that otherwise would serve to depolarize the cell membrane and thus activate (*i.e.*, open) the sodium channel: *e.g.* a high potassium chloride saline solution, or an extracellular field-stimulating electrode. The cell can then be examined to determine whether a response otherwise associated with sodium channel activation has been inhibited. In a non-limiting embodiment, the response of the cell treated with the test compound is compared to that of a control cell that has not been treated with the test compound. Cell assays include those utilizing conventional, electrode-based, electrophysiological techniques, as well as the new generation high-throughput, planar electrode (orifice) -based, electrophysiological technologies, among others. Other assays include monitoring changes in membrane potential with appropriate fluorescent, or luminescent, dyes, measuring ion flux through the sodium channel with a radiolabeled tracer, or assaying downstream consequences of sodium channel activation, such as calcium mobilization or effects on gene expression, using an appropriate reporter system.

Positive modulation (*i.e.*, agonism) of hNaIII18 subunit-containing channels may be desirable under certain circumstances, and screening for such agonists can be conducted according to the methods of the invention.

Screening

According to the present invention, nucleotide sequences encoding hNaIII18 are useful targets to identify drugs that are effective in preventing or alleviating pain, or drugs that can be used as anti-epileptics/anticonvulsants, anesthetic antiarrythmics, and in the treatment of bipolar disorder (see section entitled Therapeutics, below), any of which may be associated with the function of the sodium channel. Examples of such drugs include without limitation: (i) isolated nucleic acids capable of altering expression of hNaIII18 (*e.g.*, antisense or ribozyme molecules); (ii) small organic molecules that bind to and modulate the function of a hNaIII18 subunit or a hNaIII18 subunit-containing ion channel; and (iii) peptides or

peptide analogs that bind to and modulate the function of a hNaIII18 subunit or a hNaIII18 subunit-containing ion channel. In addition, the nucleotide sequences encoding hNaIII18 are useful for studying the role of the channels both in pain perception and in physiological and pathological brain functions.

Any screening technique known in the art can be used to screen for agonists or antagonists. The present invention contemplates screens for small molecules and mimics, as well as screens for natural products that bind to and agonize or antagonize hNaIII18-containing ion channels. For example, natural product libraries can be screened using assays of the invention for molecules that agonize or antagonize hNaIII18-containing ion channel activity.

Knowledge of the primary sequence of hNaIII18, and the similarity of that sequence with proteins of known function, can provide an initial lead to inhibitors or antagonists. Identification and screening of modulators is further facilitated by determining structural features of the protein, *e.g.*, using X-ray crystallography, neutron diffraction, nuclear magnetic resonance spectrometry, and other techniques for structure determination. These techniques provide for the rational design or identification of agonists and antagonists.

Another approach uses recombinant bacteriophage to produce large libraries. Using the "phage method" (Scott and Smith, Science 1990, 249:386-390; Cwirla, et al., Proc. Natl. Acad. Sci. USA 1990, 87:6378-6382; Devlin et al., Science 1990, 49:404-406), very large libraries can be constructed (106-108 chemical entities). A second approach uses primarily chemical methods, of which the Geysen method (Geysen et al., Molecular Immunology 1986, 23:709-715; Geysen et al. J. Immunologic Methods 1987, 102:259-274); and the method of Fodor et al. (Science 1991, 251:767-773) are examples. Furka et al. (14th International Congress of Biochemistry 1988, Volume #5, Abstract FR:013; Furka, Int. J. Peptide Protein Res. 1991, 37:487-493), Houghton (U.S. Patent No. 4,631,211) and Rutter et al. (U.S. Patent No. 5,010,175) generally describe methods to produce a mixture of peptides that can be tested as agonists or antagonists.

In another aspect, synthetic libraries, such as those described in Needels et al., Proc. Natl. Acad. Sci. USA 1993, 90:10700-4; Ohlmeyer et al., Proc. Natl. Acad. Sci. USA 1993, 90:10922-10926; Lam et al., PCT Publication No. WO

92/00252; and Kocis et al., PCT Publication No. WO 9428028, and the like, can be adapted to screen for compounds according to the present invention.

Test compounds can be screened from large libraries of synthetic or natural compounds. Numerous means are currently used for random and directed synthesis of saccharide, peptide, and nucleic acid based compounds. Synthetic compound libraries are commercially available from a variety of sources, including Maybridge Chemical Co. (Trevillet, Cornwall, UK), Comgenex (Princeton, NJ), Brandon Associates (Merrimack, NH), and Microsource (New Milford, CT). A rare chemical library is available from Aldrich (Milwaukee, WI). Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available from a variety of sources including, *e.g.*, Pan Laboratories (Bothell, WA) and MycoSearch (NC), or are readily producible de novo. Additionally, natural and synthetically produced libraries and compounds are readily modified through conventional chemical, physical, and biochemical means (see, *e.g.*, Blondelle et al., TIBTech 1996, 14:60).

In Vitro *Screening Methods and Activity Assays*

Cell-based screening

Intact cells expressing a hNaIII18 subunit-containing ion channel can be used in screening methods to identify candidate compounds useful in modulating the activity of sodium channels containing hNaIII18. In one embodiment, a cell line is established that stably expresses or overexpresses the hNaIII18 subunit protein, either alone or in combination with one or more other sodium channel β subunits, to form a functional sodium channel. Alternatively, cells (including without limitation mammalian, invertebrate, yeast, or bacterial cells) are transiently programmed to express a hNaIII18 subunit protein by introduction of the appropriate DNA or mRNA. Identification of candidate compounds can be achieved using any suitable assay, including without limitation: (i) assays that measure binding of test compounds to hNaIII18 (alone or in combination with sodium channel β subunits described *supra*): (ii) assays that measure the ability of a test compound to modulate (*i.e.*, agonize or antagonize) a measurable activity or function of hNaIII18 or a hNaIII18 subunit-containing ion channel; and (iii) assays that measure the ability of a compound to

enhance or inhibit the transcriptional activity of sequences derived from the promoter (*i.e.*, regulatory) regions of the hNaIII18 gene.

Any cell assay system that allows for assessment of functional activity of a hNaIII18 subunit-containing sodium channel is encompassed by the present invention. In a specific embodiment, described *infra*, the assay can be used to identify compounds that selectively modulate the hNaIII18 subunit protein, which can be determined by assessing the effects on NaIII18 subunit-expressing cells contacted with a test compound. The assay system can thus be used to identify compounds that selectively produce a functional effect through hNaIII18 sodium channels. Compounds that decrease activity of the sodium channel in response to activation may be useful as novel therapeutics in the amelioration of neuropathic pain mediated by DRG neurons, or as anti-epileptics/convulsants, anesthetics, antiarrythmics, or in the treatment of bipolar disorder.

Compounds that increase activity of sodium channels may be useful as cognitive enhancers, or in disorders such schizophrenia. In these instances, a subtype-selective agent would be preferable to offset the potential for proconvulsant effects and to increase cardiac contractility in individuals suffering from heart failure.

Alternatively, the change in membrane potential induced by sodium ions of the voltage-gated channel-containing cells may be monitored using fluorescence methods. When using fluorescence methods, the voltage-gated channel containing cells may be incubated with a membrane potential indicating agent that allows for a determination of changes in the membrane potential of the cells caused by the influx of sodium ions. Such membrane potential indicating agents include fluorescent indicators, such as those provided in a Molecular Devices Membrane Potential Kits for the FLIPR/Flexstation, DIBAC4(3), DiOC6(6) DiOC5(3), DiOC2(3) and fluorescence resonance energy transfer (FRET) based dyes such as JC1, and JC9, among others.

Another method that allows for assessment of functional activity of hNaIII18-containing sodium channels involves monitoring the change in membrane potential induced by sodium ions on the channel-containing cells by fluorescent methods, *e.g.*, using a FLIPR assay (Fluorescence Image Plate Reader; available from Molecular Devices)(Rose et al. Pflugers Arch. 1999 Dec;439(1-2):201-7). Another

method involves radioactive flux assays that measure the ability of radioactive tracer ions such as [^{22}Na] and [^{14}C] guanidinium to pass into the cell upon channel activation (Barann M. et al. Naunyn Schmiedebergs Arch Pharmacol. 1999; 360(3):234-41). After the channel is activated, concentrations of these tracer ions increase inside the cell. Free extra-cellular tracer is washed away, cells are lysed, and radioactivity in the lysates is counted using standard scintillation counters or other radioactivity analysis instruments.

Yet another method involves measuring cell viability upon veratridine-mediated stabilization of sodium channels in their open conformation (Okuyama K. et al., Eur J Pharmacol. 2000; 398(2):209-16). Cells undergo toxic sodium overload followed by cell death. Compounds that prevent cell death, or cellular toxicity, can be assayed with standard cytoxicity kits and with standard cell viability dyes such as alamar blue.

Cell-Free Screening

In another embodiment, an assay is a cell-free assay comprising contacting a hNaIII18 polypeptide or biologically active portion thereof with a test compound and determining the ability of the test compound to modulate (*e.g.*, stimulate or inhibit) the activity of the hNaIII18 polypeptide or biologically active portion thereof.

In yet another embodiment, the cell-free assay comprises (i) contacting the hNaIII18 polypeptide of the invention or biologically active portion thereof with a known compound or polypeptide which binds the hNaIII18 polypeptide to form an assay complex; (ii) contacting the assay complex with a test compound; (iii) determining the ability of the test compound to interact with the hNaIII18 polypeptide by determining the ability of the test compound to modulate the effect of the known compound on the activity of the sodium channel.

More specifically, a cell-free method can involve monitoring the specific binding of a radiolabeled sodium channel selective neurotoxin, such as [^{3}H]tetrodotoxin or [^{3}H]batrachotoxin, or a high affinity small-molecule ligand, to a membrane preparation from cells or tissues engineered to express hNaIII18-containing sodium channels (Garritsen A. et al. Eur J Pharmacol. 1988; 145(3):261-6;

MacKinnon AC. et al. J Pharmacol. 1995; 115(6):1103-9; Bambrick L. et al., J Pharmacol Toxicol Methods. 1994; 32(3):129-38). Following techniques that are well know in the art, total binding to membranes can be measured upon incubation with the radioligand until the biomolecular reaction reaches equilibrium. Nonspecific binding is defined in the presence of an unlabelled competitor ligand. Specific binding is the subtraction of total minus nonspecific binding. Compounds that modulate specific binding can thereby be identified.

In another embodiment, modulators of expression of the hNaIII18 polypeptide of the invention are identified in a method in which a cell is contacted with a candidate compound and the expression of the mRNA or protein corresponding to hNaIII18 in the cell is determined. The level of expression of the hNaIII18 mRNA or protein in the presence of the candidate compound is compared to the level of expression of the hNaIII18 mRNA or protein in the absence of the candidate compound. The candidate compound can thereby be identified as a modulator of expression of the hNaIII18 polypeptide of the invention based on this comparison. For example, when expression of the hNaIII18 mRNA or protein is increased in the presence of the candidate compound compared to in the absence of the candidate compound, then the candidate compound is identified as a stimulator of hNaIII18 mRNA or protein expression. Alternatively, when expression of the hNaIII18 mRNA or protein is specifically reduced in the presence of the candidate compound compared to in the absence of the candidate compound, then the candidate compound is identified as an inhibitor of hNaIII18 mRNA or protein expression. In view of this disclosure, the level of the hNaIII18 mRNA or protein expression in cells can be determined by methods known in the art.

High-Throughput Screen

Drug candidates according to the invention can be identified by screening in high-throughput assays, including without limitation cell-based or cell-free assays. It will be appreciated by those skilled in the art that different types of assays can be used to detect different types of drug candidates. Several methods of automated assays have been developed in recent years so as to permit screening of tens of thousands of compounds in a short period of time. Such high-throughput

screening methods are particularly preferred. The use of high-throughput screening assays to test for agents is greatly facilitated by the availability of the large amounts of purified hNaIII18 polypeptides provided by the invention.

Therapeutic Uses

It is desirable to modulate the function of sodium channels in a number of clinical and therapeutic environments. Sodium channels are implicated in conditions including chronic and neuropathic pain, cardiac arrhythmias (Duch et al., Toxicol Lett 1998; 100-101:255-63), neuronal disorders associated with deficient oxygen supply or mitochondrial dysfunction (Urenjak et al., Amino Acids 1998;14(1-3):151-8), and epilepsy (Ragsdale et al., Brain Res Rev 1998;26(1):16-28). In addition, inhibition of sodium channels is an effect of local anesthetics (Li et al., Mol Pharmacol 1999; 55(1):134-41).

According to the present invention, inhibition of hNaIII18 subunit-containing sodium channel activity may be used as a treatment option in patients with a pain disorder, such as but not limited to a neuropathic pain-related disease such as, *e.g.*, pain from peripheral nerve trauma, herpes virus infection, diabetes mellitus, causalgia, plexus avulsion, neuroma, limb amputation, and vasculitis. Neuropathic pain is also caused by nerve damage from chronic alcoholism, human immunodeficiency virus infection, hypothyroidism, uremia, or vitamin deficiencies. The neuronal hyperexcitability and corresponding molecular changes in neuropathic pain have many features in common with the cellular changes in certain forms of epilepsy. This has led to the use of anticonvulsant drugs for the treatment of neuropathic pain (Jensen, Eur J Pain 2002;6 Suppl A:61-8). Local anesthetics such as lidocaine and mexiletine have also be shown to inhibit TTX-S sodium channel activity in hyperexcitable neurons in rat (Novartis Found Symp 2002;241:189-201; discussion 202-5, 226-32).

Inhibition of the sodium channel of the present invention may also be used as a treatment option in patients with chronic pain. In chronic pain, the pain can be mediated by multiple mechanisms. This type of pain generally arises from injury to the peripheral or central nervous tissue. The chronic pain-type syndromes include pain associated with spinal cord injury, multiple sclerosis, post-herpetic neuralgia,

trigeminal neuralgia, phantom pain, causalgia, and reflex sympathetic dystrophy and lower back pain.

Inhibition of the sodium channel of the present invention may also be used as a treatment option in patients with nociceptive pain.

Inhibition of Protein Synthesis or Sodium Channel Activity

Gene transcription and protein translation may be inhibited by administration of exogenous compounds. Exogenous compounds may interact with extracellular and/or intracellular messenger systems to regulate protein synthesis. In this embodiment, exogenous compounds that inhibit hNaIII18 protein synthesis may be used in the prevention and/or treatment for pain resulting from persistent channel activity.

Accordingly, in an exemplary embodiment, the modulatory method of the invention involves contacting a cell, tissue or subject with an agent that modulates one or more of the activities of hNaIII18 protein activity associated with the cell. An agent that modulates hNaIII18 protein activity can be an agent as described herein, such as a nucleic acid or a protein, an hNaIII18-specific antibody, an hNaIII18 agonist or antagonist, a peptidomimetic of an hNaIII8 agonist or antagonist, or other small molecule. In one embodiment, the agent stimulates one or more hNaIII18 activities. In another embodiment the agent inhibits one or more hNaIII18 activities. Examples of such inhibitory agents include antisense hNaIII18 nucleic acid molecules, anti-hNaIII18 antibodies, and hNaIII18 inhibitors. These modulatory methods can be performed *in vitro* (*e.g.*, by culturing the cell with the agent) or, alternatively, *in vivo* (*e.g.*, by administering the agent to a subject). As such, the present invention provides methods of treating an individual afflicted with a disease or disorder characterized by aberrant or unwanted expression or activity of a hNaIII18 protein or nucleic acid molecule. In one embodiment, the method involves administering an agent (*e.g.*, an agent identified by a screening assay described herein), or combination of agents that downregulates hNaIII18 expression or activity or the activity of a hNaIII18 subunit-containing ion channel.

In yet another embodiment, the agent enhances one or more hNaIII18 activities, such as by administering a hNaIII18 protein or nucleic acid molecule as therapy to compensate for reduced or aberrant hNaIII18 expression or activity.

The present invention further provides antisense nucleic acids, which may be used to inhibit expression of hNaIII18 nucleotide sequences of the invention. This antisense technology has been described as inhibiting the peripheral tetrodotoxin (TTX)-resistant sodium channel, NaV1.8, found in sensory neurons, when administered intrathecally (Lai et al., Pain 2002; 95 (1-2):143-52). According to this method, the antisense nucleic acid, upon hybridizing under cytoplasmic conditions with complementary bases in an RNA or DNA molecule, inhibits the RNA or DNA. Additionally, hybridization of the antisense nucleic acid to the DNA or RNA may inhibit transcription of the DNA into RNA and/or translation of the RNA into the protein. If the RNA is a messenger RNA transcript, the antisense nucleic acid is a counter-transcript or mRNA-interfering complementary nucleic acid. Antisense nucleic acid molecules can be encoded by a recombinant gene for expression in a cell (see, *e.g.,* U.S. Patent No. 5,814,500; U.S. Patent No. 5,811,234) or can be prepared synthetically (*e.g.,* U.S. Patent No. 5,780,607).

Alternatively, antibody molecules or antigen-binding antibody fragments can be administered either directly or by expressing nucleotide sequences encoding antibodies or binding fragments thereof within the target cell population by utilizing, for example, techniques such as those described in Marasco *et al.* (Proc. Natl. Acad Sci. USA, 1993, 90:7889-7893).

Formulations and Administration

The drug candidate or agent that modulates hNaIII18 activity is advantageously formulated in a pharmaceutical composition by admixing the drug candidate or agent with a pharmaceutically acceptable carrier. This agent may then be designated as the active ingredient, or therapeutic agent for use, for example, against chronic, neuropathic pain, or nociceptive pain

The form, amount and route of administration of the therapeutic compound envisioned for use depends on the type and severity of the disease or condition to be treated, as well as the patient's state of health, gender, weight, age,

etc., and can be determined by an attending medical practitioner in view, *e.g.*, of the results of published clinical trials. The concentration or amount of the active ingredient depends on the desired dosage and administration regimen, as discussed below. Suitable dose ranges may include from about 1 mg/kg to about 100 mg/kg of body weight per day.

The pharmaceutical compositions may also include other biologically active substances in combination with the NaIII18 modulatory agent. Such substances include but are not limited to opioids such as morphine, codeine, fentynyl, oxycodone, hydrocodone, and buprenorphine; and non-steroidal anti-inflammatory drugs (NSAID's) such as but not limited to ibuprofen and COX-2 inhibitors, among others

The phrase "pharmaceutically acceptable" refers to molecular entities and compositions that are physiologically tolerable and do not typically produce an allergic or similar untoward reaction, such as gastric upset, dizziness and the like, when administered to a human. Preferably, as used herein, the term "pharmaceutically acceptable" means that the carrier has been approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the active ingredient is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water or aqueous solution saline solutions and aqueous dextrose and glycerol solutions are preferably employed as carriers, particularly for injectable solutions. Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin.

According to the invention, the pharmaceutical composition of the invention can be introduced parenterally, transmucosally, *e.g.*, orally (per os), nasally, rectally, or transdermally. Parental routes include intravenous, intra-arteriole, intramuscular, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial administration. The pharmaceutical composition may alternatively be

adapted for topical or transdermal application, such in a salve, cream, lotion, spray or transdermal patch system.

The pharmaceutical compositions may be added to a retained physiological fluid such as blood or synovial fluid. For CNS (Central Nervous System) administration, a variety of techniques are available for promoting transfer of the therapeutic across the blood brain barrier including disruption by surgery or injection, co-administration of drugs that transiently open adhesion contact between CNS vasculature endothelial cells, and co-administration of substances that facilitate translocation through such cells.

In another embodiment, the active ingredient can be delivered in a vesicle, in particular a liposome (see Langer, Science 1990; 249:1527-1533; Treat et al., in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss: New York 1989 pp. 353-365; Lopez-Berestein, ibid., pp. 317-327; see generally ibid.).

In yet another embodiment, the therapeutic substance can be delivered in a controlled release formulation. For example, an active ingredient may be administered using intravenous infusion with a continuous pump, in a polymer matrix such as poly-lactic/glutamic acid (PLGA), a pellet containing a mixture of cholesterol and the active ingredient (SilasticRTM; Dow Corning, Midland, MI; see U.S. Patent No. 5,554,601) implanted subcutaneously, an implantable osmotic pump, a transdermal patch, liposomes, or other modes of administration.

Compounds identified in the screening methods described herein (*i.e.*, modulators of sodium channel activity), may be provided to the patient in formulations that are known in the art and may include any pharmaceutically acceptable additives, such as excipients, lubricants, diluents, flavorants, colorants, and disintegrants. The formulations may be produced in useful dosage units such as tablet, caplet, capsule, liquid, or injection. In a further embodiment, these compounds are also administered in conjunction with other therapeutic agents such as the local anesthetics and anti-epileptic or anti-convulsants discussed *supra*.

The form and amount of therapeutic compound envisioned for use depends on the type of disease and the severity of the desired effect, patient state, etc., and can be determined by one skilled in the art.

EXAMPLES

The present invention is also described by means of an example, presented below. The use of such an example is illustrative only and in no way limits the scope and meaning of the invention or of any exemplified term. Likewise, the invention is not limited to any particular preferred embodiments described herein. Indeed, many modifications and variations of the invention will be apparent to those skilled in the art upon reading this specification and can be made without departing from its spirit and scope. The invention is therefore encompassed by the appended claims along with the full scope of equivalents to which the claims are entitled.

EXAMPLE 1: CLONING AND EXPRESSION OF HUMAN NaIII18

Methods

Reverse transcription and amplification of hNaIII18 cDNA. Reverse transcription was carried out using ThermoScript Reverse Transcriptase (Life Technologies, Rockville, MD), at an annealing temperature of 55°C to maximize the likelihood of obtaining a full-length mRNA, according to manufacturer's instructions.

The following primers were designed to amplify the resulting full-length hNaIII18 cDNA:

forward primer (SEQ ID NO: 7)	5' - ATAAGAATGCGGCCGCTGAAAAGATGGCACAGGCAC-3'
reverse primer (SEQ ID NO: 8)	5' - ATAGTTTAGCGGCCGCCTTGAAGTCCAGTTGACACA -3'

Primers were designed from the human NaIII (SCN3A) mRNA sequence previously identified (GenBank Accession # AJ251507).

Full-length cDNA (6000 base-pairs) was amplified using the Expand Long Template PCR (Boehringer Mannheim, Indianapolis, IA) according to the manufacturer's instructions. This enzyme is a mixture of thermostable Taq and Pwo

DNA polymerases. The number of cycles used for amplification was decreased to 28 cycles instead of the traditional 30-35 as an added precaution to minimize the occurrence of mutations during PCR.

Purification and cloning of PCR products into expression vectors. PCR products resulting from the above-described reaction were visualized after electrophoresis on an agarose gel containing Crystal Violet. DNA was purified from the gel using methods well known in the art. DNA was stored in Tris-EDTA buffer, pH 7.4.

The PCR-amplified cDNA was cloned into a low-copy number expression vector, pLCTM1 (kindly provided by Al Goldin, UCI) according to standard procedures. This vector is under the control of the origin of replication (ORI) from plasmid pACYC184, which has a limited number of replication cycles, resulting in a decreased error rate during DNA replication.

Further, the plasmid contains a tetracycline-resistance gene instead of an ampicillin-resistance gene for selection. Tetracycline is less likely to induce mutations than ampicillin during selection. The plasmid also contains a neomycin resistant gene (NeoR) for selection of stable cell lines using the neomycin analog G418.

Once cloned, the vectors were transformed into maximum efficiency STBL2 competent *E. coli* bacteria (Life Technologies, Rockville, MD), provided in the kit according to manufacturer's instructions. These cells optimize the cloning of unstable inserts. Bacteria expressing hNaIII18 were grown at 30-33 °C, and maintained in exponential (log) growth phase for the duration of culture.

Small tetracycline-resistant colonies were selected and grown-up for small-scale DNA preparations and large-scale preparations. The concentration of tetracycline was kept low (15 μg/ml) to further minimize adverse growth conditions. The cDNA was extracted using the Wizard Plus SV Minipreps DNA Purification System Kit (Promega, Madison, WI) according to the manufacturer's instructions, or Qiagen Midipreps according to manufacturer's instructions (Qiagen, Valencia, CA). cDNA was then analyzed by restriction digest, and partial sequencing. Full sequencing was performed by MWG (North Carolina). Partial sequencing was done with standard DTCS sequencing method using a commercial Beckman Coulter kit.

Transient and stable transfection. In order to identify functional clones, human embryonic kidney cells (HEK293) were transiently transfected with clones that were identified as having the correct insert, and surveyed by an electrophysiological assay (Fugene transfection reagent, according to manufacturer's recommendation). One clone, pLCTM1huNaIII-18, was determined to be functional as it gave large TTX-S currents with the expected activation and inactivation kinetics typical of NaIII channel. For example, typical activation is measured within fractions of ms at Vm=0mV (corresponding Imax). Inactivation is measured as the time constant between 1-3 ms at Vm=0mV (increasing to 20 ms at -50 mV to 0.5 ms at +40mV). Recovery from inactivation is a time constant of about 10ms at Vm=-100mV and 60 ms at -80mV (see *e.g.*, Cummins et al., J Neurosci 2001; 21:52-5961).

This clone was fully sequenced for confirmation. In addition, several non-functional clones were partially sequenced.

Clone pLLCTM1huNaIII-18 was used to generate a stable cell line in HEK293 cells. Fugene-mediated transfection of HEK cells was performed in 35 mm dish followed by G418 selection (300 and 500 μg/ml), colony isolation, line expansion. G418-resistant cells were then analyzed with immunocytochemistry, RT-PCR and electrophysiology according to standard techniques.

Electrophysiology. Stably transfected cells were grown on poly DL-lysine-coated glass coverslips at ~2,000 cells/slip, or Petri dishes at ~10,000 cells/dish and were then placed into the electrophysiology recording chamber and infused with an extracellular solution (140 mM NaCl, 4.7 mM KCl, 1.2 mM $MgCl_2$, 1 mM $CaCl_2$, 11 mM glucose and 5 mM HEPES, pH 7.4) at a rate of 2 ml/min. Electrodes were prepared by pulling Patch pipettes (borosilicate glass) using a Sutter P-97 electrode puller, and were filled with a solution containing 110 mM CsCl, 10 mM NaCl, 5 mM $MgCl_2$, 11 mM EGTA, 10 mM HEPES, 2 mM ATP and 1 mM GTP, pH 7.25, osmolarity 275-290 mOsm. When filled with this solution, the electrodes had resistances of about 1-4 MΩ. Currents were recorded using a whole-cell voltage clamp techniques as described in Hamill et al. (Pflugers Arch. 1981; 391; 85-100), at room temperature (21-23 °C). Briefly, currents were recorded using an Axopatch 200A amplifier (Axon Instruments, Foster City, CA) and were leak-subtracted (P/4),

low-pass filtered (3 kHz, 8-pole Bessel), digitized (20-50-μs intervals), and stored using Digidata 1200 B interface and Pclamp6/Clampex software (Axon Instruments, Foster City, CA). Residual series access resistance was largely (75-80%) canceled using built-in amplifier circuitry. The junction potential calculated using JPCalcW software (Cell MicroControl, Virginia Beach, VA) was small (<7 mV); so, no correction of the holding voltage was made.

To take I-V curves, cells were held at a holding voltage, V_h = -90mV. A series of 16 depolarizing pulses (10ms in duration) incrementing in 10 mV steps were applied at a frequency of 0.5 Hz. The peak values of currents were plotted against corresponding voltage steps to get the I-V curve. From this plot V_{max}, *i.e.*, the voltage causing the maximal Na^+ current, as well as rising times to peak and time constant for inactivation at different voltages were determined. To get steady-state inactivation curves, cells were held at a holding voltage, V_h = -120mV to remove residual inactivation. A series of 30 depolarizing conditioning pre-pulses (each 100ms in duration) incrementing in 5 mV steps immediately followed by a 5 ms testing pulse, V_t, to V_{max} were applied at a frequency of 0.5 Hz. The peak currents in response to V_t were plotted against the size of corresponding conditioning pre-pulses, V_c, to get steady-state inactivation curve. The Boltzman fit to this curve, *i.e.*, $\{1/[1+\exp((V+ V½) /k)]\}$, returned the values of V½ (the half-inactivation voltage) and k (the slope of the curve).

To measure recovery from inactivation, cells were held at a holding voltage

V_h = -120mV to remove residual steady-state inactivation. The depolarizing conditioning pre-pulse (100 ms in duration) was applied to V_c to cause complete inactivation of the channels (usually V_c=-10 mV) . The conditioning pre-pulse was immediately followed by hyperpolarizing gap back to -120mV of a variable duration. The gap duration was incremented in subsequent cycles in varying steps (2 ms -100 ms) depending on the speed of recovery. The gap was immediately followed by the testing pulse V_t (10 ms in length) to assess the fraction of Na^+ channels available for activation. The cycle was repeated every 5 seconds while the gap duration was incremented. The peak currents to V_t were plotted against the corresponding gap

duration to get the kinetics of recovery. The mono- or double- exponential fit to the data returned the time constant, $\tau_{repr.}$, of repriming from inactivation.

Results

Identification of a splice-variant for human NaIII (SCN3). Clone pLCM1huNaIII-18 is a novel splice variant and contains an additional 147 nucleotides corresponding to 49 amino acids in the cytoplasmic loop between domain 1S6 and IIS1 (see SEQ ID NO: 1 and SEQ ID NO: 2). Partial sequencing of several other clones that were not determined to have functional activity revealed sequences that either matched the published sequence (GenBank Accession #AJ251507) or contained an extra 9 or 96 nucleotides. The shorter splicing patterns correspond to what had been described for the rat NaIII clone (Schaller et al., *J Neurosci* 1992; 12(4):1370-81), resulting in a protein with an additional 3 (rNaIIIa) or 22 (rNaIIIb) amino acids, but had not been described for the human NaIII before.

Subsequent to the completion of the cloning of hNaIII18, it was discovered that a clone having the same 147 nucleotide insert was deposited in GenBank on February 1, 2001 (GenBank Accession # AF225986-SEQ ID NO: 5). See cDNA alignment in Figure 8. However, that encoded amino acid sequence differs from the sequence disclosed herein by 12 amino acids (between two clones), at amino acid residues 208, 475, 495, 508, 604,1163, 1576, 1614, 1741, 1743, 1862 and 1966, respectively (SEQ ID NO: 2 vs. SEQ ID NO: 6). See amino acid aligment of Figure 9.

Stable transfection of the pLCM1huNaIII-18 resulted in the generation of two cell lines that expressed the expected ~220 kDa hNaIII18 protein and exhibited functional sodium channels, designated 293/huNaIII18-300-20 and 293/huNaIII18-500-35, with appropriate TTX-S currents. 293/huNaIII18-300-20 had an activation threshold voltage of -40 mV (Figure 9A), a steady state V ½ inactivation voltage of -58 mV (Figure 9B), a recovery time after inactivation of 2.5 ms (fast component) AND 113 ms (slow component-(Figure 9C), and inactivation kinetics of 0.8 ms (Figure 9D).

****

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

Patents, patent applications, publications, procedures, and the like are cited throughout this application, the disclosures of which are incorporated herein by reference in their entireties.

WHAT IS CLAIMED IS:

1. An isolated nucleic acid comprising a nucleotide sequence encoding a polypeptide
having the amino acid sequence of Figure 2 (SEQ ID NO: 2).

2. The isolated nucleic acid of claim 1, comprising the nucleotide sequence of Figure 1 (SEQ ID NO: 1).

3. A recombinant vector comprising a nucleotide sequence encoding a polypeptide having the amino acid sequence of Figure 2 (SEQ ID NO:2).

4. A host cell comprising the recombinant vector of claim 3.

5. A host cell genetically engineered to comprise the nucleic acid of claim 1.

6. The host cell of claim 5 which is eukaryotic.

7. A eukaryotic host cell genetically engineered to express, or overexpress, a polypeptide having the amino acid sequence of Figure 2 (SEQ ID NO: 2).

8. A method for expressing a polypeptide in a cell cultured *in vitro* comprising culturing the cell of claim 4, 5, 6 or 7 under conditions conducive to the expression of the polypeptide comprising the amino acid sequence of Figure 2 (SEQ ID NO:2).

9. An isolated polypeptide comprising the amino acid sequence of Figure 2 (SEQ ID NO:2).

10. A host cell genetically engineered to co-express a polypeptide comprising the amino acid sequence of Figure 2 (SEQ ID NO:2) and a β-subunit of a sodium channel selected from the group consisting of β1, β2, and β3.

11. An antibody or antigen-binding fragment that specifically binds to a polypeptide having the amino acid sequence of Figure 2 (SEQ ID NO: 2).

12. The antibody of claim 11, which is a monoclonal antibody.

13. A method for detecting expression in a sample of a polypeptide comprising the amino acid sequence of Figure 2 (SEQ ID NO:2), which method comprises detecting specific binding of the antibody or antigen-binding fragment of claim 11 to a polypeptide in the sample.

14. A method for identifying a test compound that binds to a sodium channel comprising a polypeptide comprising the amino acid sequence of Figure 2 (SEQ ID NO:2), which method comprises:

(i) contacting a host cell that expresses a sodium channel comprising a polypeptide comprising the amino acid sequence of Figure 2 (SEQ ID NO:2) with a test compound; and

(ii) determining whether the test compound binds to the host cell but not to a control cell that does not express a sodium channel comprising a polypeptide comprising the amino acid sequence of Figure 2 (SEQ ID NO:2).

15. An assay method for identifying a test compound that modulates the activity of a sodium channel comprising a polypeptide comprising the amino acid sequence of Figure 2 (SEQ ID NO:2), which method comprises:

(i) providing a host cell that expresses a functional sodium channel comprising at least one polypeptide comprising the amino acid sequence of Figure 2 (SEQ ID NO:2),

(ii) contacting the host cell with a test compound under conditions that would activate sodium channel activity of said functional sodium channel in the absence of

the test compound; and

(iii) determining whether the host cell contacted with the test compound exhibits a modulation in activity of the functional sodium channel.

16. The assay method of claim 15, wherein the host cell has been genetically engineered to express or overexpress the functional sodium channel.

17. The assay method of claim 15, wherein the host cell has been genetically engineered by the introduction into the cell of a nucleic acid molecule having a nucleotide sequence encoding a polypeptide comprising the amino acid sequence of Figure 2 (SEQ ID NO:2).

18. The assay method of claim 15, wherein the host cell has been genetically engineered to upregulate the expression of a nucleic acid encoding a polypeptide comprising the amino acid sequence of Figure 2 (SEQ ID NO:2),

19. The assay method of claim 18, wherein the upregulated nucleic acid is endogenous to the host cell.

20. The assay method of claim 15, wherein the modulation of the functional sodium channel activity is antagonism of that activity.

21. The assay method of claim 15, wherein the modulation of the functional sodium channel activity is agonism of that activity.

FIGURE 1: NaIII18 cDNA (SEQ ID NO: 1)

tgaaaagatggcacaggcactgttggtacccccaggacctgaaagcttccgccttttttactaga
gaatctcttgctgctatcgaaaaacgtgctgcagaagagaaagccaagaagcccaaaaaggaac
aagataatgatgatgagaacaaaccaaagccaaatagtgacttggaagctggaaagaaccttcc
atttatttatggagacattcctccagagatggtgtcagagcccctggaggacctggatccctac
tatatcaataagaaaacttttatagtaatgaataaaggaaaggcaattttccgattcagtgcca
cctctgccttgtatattttaactccactaaaccctgttaggaaaattgctatcaagattttggt
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agcaaccctcctgactggacaaagaatgtagagtacacattcactggaatctataccttttgagt
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gaactggctggatttcagtgtcattgtgatggcgtatgtaacagaatttgtaagcctaggcaat
gtttcagcccttcgaactttcagagtcttgagagctctgaaaactatttctgtaattccaggtt
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tgtgttctgtctgagcgtgtttgctctcattgggctgcagctgttcatgggcaatctgaggaat
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gcacaatggattcaaatgggacatttgttaatgtaacaatgagcacatttaactggaaggatta
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atggctacacaagctttgacacctttagctgggctttcctgtctctatttcgactcatgactca
agattactgggaaaatctttaccagttgacattacgtgctgctgggaaaacatacatgatattt
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gcaccttgaaggaaacaacaaaggagagagagacagctttcccaaatccgaatctgaagacagc
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gctcccctcatcagtctctcttgagtatccgtggctccctgttttccccaagacgcaatagcaa
aacaagcattttcagtttcagaggtcgggcaaaggatgttggatctgaaaatgactttgctgat
gatgaacacagcacatttgaagacagcgaaagcaggagagactcactgtttgtgccgcacagac
atggagagcgacgcaacagtaacgttagtcaggccagtatgtcatccaggatggtgccagggct
tccagcaaatgggaagatgcacagcactgtggattgcaatggtgtggtttccttggtgggtgga
ccttcagctctaacgtcacctactggacaacttcccccagagggcaccaccacagaaacggaag
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cactatttgcattgtcttaaataccctctttatggccatggagcactaccccatgactgagcaa
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aatgatgactgtacgctcccacggtggcacatgaacgacttcttccactccttcctgattgtgt

FIGURE 1 (continued)

tccgcgtgctgtgtggagagtggatagagaccatgtgggactgtatggaggtcgctggccaaac
catgtgccttattgttttcatgttggtcatggtcattggaaaccttgtggttctgaacctcttt
ctggccttattgttgagttcatttagctcagacaaccttgctgctactgatgatgacaatgaaa
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gagatgggaatggaaccaccagtggtgtaggtactggaagcagtgttgaaaaatacgtaatcga
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ggagagtctgactttgaaaacttaaatactgaagagttcagcagtgagtcagaactagaagaaa
gcaaagagaaattaaatgcaaccagctcatctgaaggaagcacagttgatgttgttctaccccg
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catgatccttctcagtagtggtgcattggcctttgaagatatatacattgaacagcgaaagact
atcaaaaccatgctagaatatgctgacaaagtctttacctatatattcattctggaaatgcttc
tcaaatgggttgcttatggatttcaaacatatttcactaatgcctggtgctggctagatttctt
gatcgttgatgtttctttggttagcctggtagccaatgctcttggctactcagaactcggtgcc
atcaaatcattacggacattaagagctttaagacctctaagagccttatcccggtttgaaggca
tgagggtggttgtgaatgctcttgttggagcaattccctctatcatgaatgtgctgttggtctg
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gattcacgagatgttaaacttcagcctgtatatgaagaaaatctgtacatgtatttatactttg
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agcttattgccatggatctgcccatggtcagtggtgaccggatccactgtcttgatattttatt
tgcctttacaaagcgtgttttgggtgagagtggagagatggatgcccttcgaatacagatggaa
gacaggtttatggcatcaaacccctccaaagtctcttatgagcctattacaaccactttgaaac

FIGURE 1 (continued)

gtaaacaagaggaggtgtctgccgctatcattcagcgtaatttcagatgttatcttttaaagca
aaggttaaaaaatatatcaagtaactataacaaagaggcaattaaagggaggattgacttacct
ataaaacaagacatgattattgacaaactaaatgggaactccactccagaaaaaacagatggga
gttcctctaccacctctcctccttcctatgatagtgtaacaaaaccagacaaggaaaagtttga
gaaagacaaaccagaaaaagaaagcaaaggaaaagaggtcagagaaaatcaaaagtaaaaagaa
acaaagaattatctttgtgatcaattgtttacagcctatga

FIGURE 2: NaIII18 amino acid (SEQ ID NO: 2)

MAQALLVPPGPESFRLFTRESLAAIEKRAAEEKAKKPKKEQDNDDENKPKPNSDLEAG
KNLPFIYGDIPPEMVSEPLEDLDPYYINKKTFIVMNKGKAIFRFSATSALYILTPLNPVR
KIAIKILVHSLFSMLIMCTILTNCVFMTLSNPPDWTKNVEYTFTGIYTFESLIKILARGF
CLEDFTFLRDPWNWLDFSVIVMAYVTEFVSLGNVSALRTFRVLRALKTISVIPGLKTIVG
ALIQSVKKLSDVMILTVFCLSVFALIGLQLFMGNLRNKCLQWPPSDSAFETNTTSYFNGT
MDSNGTFVNVTMSTFNWKDYIGDDSHFYVLDGQKDPLLCGNGSDAGQCPEGYICVKAGRN
PNYGYTSFDTFSWAFLSLFRLMTQDYWENLYQLTLRAAGKTYMIFFVLVIFLGSFYLVNL
ILAVVAMAYEEQNQATLEEAEQKEAEFQQMLEQLKKQQEEAQAVAAASAASRDFSGIGGL
GELLESSSEASKLSSKSAKEWRNRRKKRRRREHLEGNNKGERDSFPKSESEDSVKRSSFL
FSMDGNRLTSDKKFCSPHQSLLSIRGSLFSPRRNSKTSIFSFRGRAKDVGSENDFADDEH
STFEDSESRRDSLFVPHRHGERRNSNVSQASMSSRMVPGLPANGKMHSTVDCNGVVSLVG
GPSALTSPTGQLPPEGTTTETEVRKRRLSSYQISMEMLEDSSGRQRAVSIASILTNTMEE
LEESRQKCPPCWYRFANVFLIWDCCDAWLKVKHLVNLIVMDPFVDLAITICIVLNTLFMA
MEHYPMTEQFSSVLTVGNLVFTGIFTAEMVLKIIAMDPYYYFQEGWNIFDGIIVSLSLME
LGLSNVEGLSVLRSFRLLRVFKLAKSWPTLNMLIKIIGNSVGALGNLTLVLAIIVFIFAV
VGMQLFGKSYKECVCKINDDCTLPRWHMNDFFHSFLIVFRVLCGEWIETMWDCMEVAGQT
MCLIVFMLVMVIGNLVVLNLFLALLLSSFSSDNLAATDDDNEMNNLQIAVGRMQKGIDYV
KNKMRECFQKAFFRKPKVIEIHEGNKIDSCMSNNTGIEISKELNYLRDGNGTTSGVGTGS
SVEKYVIDENDYMSFINNPSLTVTVPIAVGESDFENLNTEEFSSESELEESKEKLNATSS
SEGSTVDVVLPREGEQAETEPEEDLKPEACFTEGCIKKFPFCQVSTEEGKGKIWWNLRKT
CYSIVEHNWFETFIVFMILLSSGALAFEDIYIEQRKTIKTMLEYADKVFTYIFILEMLLK
WVAYGFQTYFTNAWCWLDFLIVDVSLVSLVANALGYSELGAIKSLRTLRALRPLRALSRF
EGMRVVVNALVGAIPSIMNVLLVCLIFWLIFSIMGVNLFAGKFYHCVNMTTGNMFDISDV
NNLSDCQALGKQARWKNVKVNFDNVGAGYLALLQVATFKGWMDIMYAAVDSRDVKLQPVY
EENLYMYLYFVIFIIFGSFFTLNLFIGVIIDNFNQQKKKFGGQDIFMTEEQKKYYNAMKK
LGSKKPQKPIPRPANKFQGMVFDFVTRQVFDISIMILICLNMVTMMVETDDQGKYMTLVL
SRINLVFIVLFTGEFVLRLVSLRHYYFTIGWNIFDFVVVILSIVGMFLAEMIEKYFVSPT
LFRVIRLARIGRILRLIKGAKGIRTLLFALMMSLPALFNIGLLLFLVMFIYAIFGMSNFA
YVKKEAGIDDMFNFETFGNSMICLFQITTSAGWDGLLAPILNSAPPDCDPDTIHPGSSVK
GDCGNPSVGIFFFVSYIIISFLVVVNMYIAVILENFSVATEESAEPLSEDDFEMFYEVWE
KFDPDATQFIEFSKLSDFAAALDPPLLIAKPNKVQLIAMDLPMVSGDRIHCLDILFAFTK
RVLGESGEMDALRIQMEDRFMASNPSKVSYEPITTTLKRKQEEVSAAIIQRNFRCYLLKQ
RLKNISSNYNKEAIKGRIDLPIKQDMIIDKLNGNSTPEKTDGSSSTTSPPSYDSVTKPDK
EKFEKDKPEKESKGKEVRENQK

10/537761

FIGURE 3: cDNA sequence of human SCN3A of Clare et al. (SEQ ID NO: 3)

```
   1 taccctaacc atcttggatg ctgggctttg ttatgctgta attcataagg ctctgtttta
  61 tcagagatta tggagcaaga aaactgaagc caagccacat caaggtttga cagggatgag
 121 atacctgtca aggattcata gtagagtggc ttactgggaa aggagcaaag aatctcttct
 181 agggatattg taagaataaa tgagataatt cacagaaggg acctggagct tttccggaaa
 241 aaggtgctgt gactatctaa ggtaattcgt atgcaagaag ctacacgtaa ttaaatgtgc
 301 aggatgaaaa gatggcacag gcactgttgg tacccccagg acctgaaagc ttccgccttt
 361 ttactagaga atctcttgct gctatcgaaa aacgtgctgc agaagagaaa gccaagaagc
 421 ccaaaaagga acaagataat gatgatgaga acaaaccaaa gccaaatagt gacttggaag
 481 ctggaaagaa ccttccattt atttatggag acattcctcc agagatggtg tcagagcccc
 541 tggaggacct ggatccctac tatatcaata agaaaacttt tatagtaatg aataaaggaa
 601 aggcaatttt ccgattcagt gccacctctg ccttgtatat tttaactcca ctaaaccctg
 661 ttaggaaaat tgctatcaag attttggtac attctttatt cagcatgctt atcatgtgca
 721 ctattttgac caactgtgta tttatgacct tgagcaaccc tcctgactgg acaaagaatg
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 841 ggttttgctt agaagatttt acgtttcttc gtgatccatg gaactggctg gatttcagtg
 901 tcattgtgat ggcgtatgta acagaatttg taagcctagg caatgtttca gcccttcgaa
 961 ctttcagagt cttgagagct ctgaaaacta tttctgtaat tccaggttta aagaccattg
1021 tgggggccct gatccagtcg gtaaagaagc tttctgatgt gatgatcctg actgtgttct
1081 gtctgagcgt gtttgctctc attgggctgc agctgttcat gggcaatctg aggaataaat
1141 gtttgcagtg gcccccaagc gattctgctt ttgaaaccaa caccacttcc tactttaatg
1201 gcacaatgga ttcaaatggg acatttgtta atgtaacaat gagcacattt aactggaagg
1261 attacattgg agatgacagt cacttttatg ttttggatgg gcaaaaagac cctttactct
1321 gtggaaatgg ctcagatgca ggccagtgtc cagaaggata catctgtgtg aaggctggtc
1381 gaaaccccaa ctatggctac acaagctttg acacctttag ctgggctttc ctgtctctat
1441 ttcgactcat gactcaagac tactgggaaa atctttacca gttgacatta cgtgctgctg
1501 ggaaaacata catgatattt tttgtcctgg tcatttttctt gggctcattt tatttggtga
1561 atttgatcct ggctgtggtg gccatggcct atgaggagca gaatcaggcc accttggaag
1621 aagcagaaca aaaagaggcc gaatttcagc agatgctcga acagcttaaa aagcaacagg
1681 aagaagctca ggcagttgcg gcagcatcag ctgcttcaag agatttcagt ggaataggtg
1741 ggttaggaga gctgttggaa agttcttcag aagcatcaaa gttgagttcc aaaagtgcta
1801 aagaatggag gaaccgaagg aagaaaagaa gacagagaga gcaccttgaa ggaaacaaca
1861 aaggagagag agacagcttt cccaaatccg aatctgaaga cagcgtcaaa agaagcagct
1921 tccttttctc catggatgga aacagactga ccagtgacaa aaaattctgc tcccctcatc
1981 agtctctctt gagtatccgt ggctccctgt tttccccaag acgcaatagc aaaacaagca
2041 ttttcagttt cagaggtcgg gcaaaggatg ttggatctga aaatgacttt gctgatgatg
2101 aacacagcac atttgaagac agcgaaagca ggagagactc actgtttgtg ccgcacagac
2161 atggagagcg acgcaacagt aacggcacca ccactgaaac ggaagtcaga aagagaaggt
2221 taagctctta ccagatttca atggagatgc tggaggattc ctctggaagg caaagagccg
2281 tgagcatagc cagcattctg accaacacaa tggaagaact tgaagaatct agacagaaat
2341 gtccgccatg ctggtataga tttgccaatg tgttcttgat ctgggactgc tgtgatgcat
2401 ggttaaaagt aaaacatctt gtgaatttaa ttgttatgga tccatttgtt gatcttgcca
2461 tcactatttg cattgtctta aataccctct ttatggccat ggagcactac cccatgactg
2521 agcaattcag tagtgtgttg actgtaggaa acctggtctt tactgggatt ttcacagcag
2581 aaatggttct caagatcatt gccatggatc cttattacta tttccaagaa ggctggaata
2641 tctttgatgg aattattgtc agcctcagtt taatggagct tggtctgtca aatgtggagg
2701 gattgtctgt actgcgatca ttcagactgc ttagagtttt caagttggca aaatcctggc
2761 ccacactaaa tatgctaatt aagatcattg gcaattctgt gggggctcta ggaaacctca
2821 ccttggtgtt ggccatcatc gtcttcattt ttgctgtggt cggcatgcag ctctttggta
2881 agagctacaa agaatgtgtc tgcaagatca atgatgactg tacgctccca cggtggcaca
2941 tgaacgactt cttccactcc ttcctgattg tgttccgcgt gctgtgtgga gagtggatag
3001 agaccatgtg ggactgtatg gaggtcgctg gccaaaccat gtgccttatt gttttcatgt
3061 tggtcatggt cattggaaac cttgtggttc tgaacctctt tctggcctta ttgttgagtt
3121 catttagctc agacaacctt gctgctactg atgatgacaa tgaaatgaat aatctgcaga
```

FIGURE 3 (continued)

3181 ttgcagtagg aagaatgcaa aagggaattg attatgtgaa aaataagatg cgggagtgtt
3241 tccaaaaagc ctttttaga aagccaaaag ttatagaaat ccatgaaggc aataagatag
3301 acagctgcat gtccaataat actggaattg aaataagcaa agagcttaat tatcttagag
3361 atgggaatgg aaccaccagt ggtgtaggta ctggaagcag tgttgaaaaa tacgtaatcg
3421 atgaaaatga ttatatgtca ttcataaaca accccagcct caccgtcaca gtgccaattg
3481 ctgttggaga gtctgacttt gaaaacttaa atactgaaga gttcagcagt gagtcagaac
3541 tagaagaaag caaagagaaa ttaaatgcaa ccagctcatc tgaaggaagc acagttgatg
3601 ttgttctacc ccgagaaggt gaacaagctg aaactgaacc cgaagaagac cttaaaccgg
3661 aagcttgttt tactgaagga tgtattaaaa agtttccatt ctgtcaagta agtacagaag
3721 aaggcaaagg gaagatctgg tggaatcttc gaaaaacctg ctacagtatt gttgagcaca
3781 actggtttga gactttcatt gtgttcatga tccttctcag tagtggtgca ttggcctttg
3841 aagatatata cattgaacag cgaaagacta tcaaaaccat gctagaatat gctgacaaag
3901 tctttaccta tatattcatt ctggaaatgc ttctcaaatg ggttgcttat ggatttcaaa
3961 catatttcac taatgcctgg tgctggctag atttcttgat cgttgatgtt tctttggtta
4021 gcctggtagc caatgctctt ggctactcag aactcggtgc catcaaatca ttacggacat
4081 taagagcttt aagacctcta agagccttat cccggtttga aggcatgagg gtggttgtga
4141 atgctcttgt tggagcaatt ccctctatca tgaatgtgct gttggtctgt ctcatcttct
4201 ggttgatctt tagcatcatg ggtgtgaatt tgtttgctgg caagttctac cactgtgtta
4261 acatgacaac gggtaacatg tttgacatta gtgatgttaa caatttgagt gactgtcagg
4321 ctcttggcaa gcaagctcgg tggaaaaacg tgaaagtaaa ctttgataat gttggcgctg
4381 gctatcttgc actgcttcaa gtggccacat ttaaaggctg gatggatatt atgtatgcag
4441 ctgttgattc acgagatgtt aaacttcagc ctgtatatga agaaaatctg tacatgtatt
4501 tatactttgt catctttatc atctttgggt cattcttcac tctgaatcta ttcattggtg
4561 tcatcataga taacttcaac cagcagaaaa agaagtttgg aggtcaagac atctttatga
4621 cagaggaaca gaaaaaatat tacaatgcaa tgaagaaact tggatccaag aaacctcaga
4681 aacccatacc tcgcccagca aacaaattcc aaggaatggt ctttgatttt gtaaccagac
4741 aagtctttga tatcagcatc atgatcctca tctgcctcaa catggtcacc atgatggtgg
4801 aaacggatga ccagggcaaa tacatgaccc tagttttgtc ccggatcaac ctagtgttca
4861 ttgttctgtt cactggagaa tttgtgctga agctcgtctc cctcagacac tactacttca
4921 ctataggctg gaacatcttt gactttgtgg tggtgattct ctccattgta ggtatgtttc
4981 tggctgagat gatagaaaag tattttgtgt cccctacctt gttccgagtg atccgtcttg
5041 ccaggattgg ccgaatccta cgtctgatca aaggagcaaa ggggatccgc acgctgctct
5101 ttgctttgat gatgtcccct cctgcgttgt ttaacatcgg cctcctgctc ttcctggtca
5161 tgtttatcta tgccatcttt gggatgtcca actttgccta tgttaaaaag gaagctggaa
5221 ttgatgacat gttcaacttt gagacctttg gcaacagcat gatctgcttg ttccaaatta
5281 caacctctgc tggctgggat ggattgctag cacctattct taatagtgca ccacccgact
5341 gtgaccctga cacaattcac cctggcagct cagttaaggg agactgtggg aacccatctg
5401 ttgggatttt ctttttcgtc agttacatca tcatatcctt cctggttgtg gtgaacatgt
5461 acatcgcggt catcctggag aacttcagtg ttgctactga agaaagtgca gagcccctga
5521 gtgaggatga ctttgagatg ttctatgagg tttgggaaaa gtttgatccc gatgcgaccc
5581 agtttataga gttctctaaa ctctctgatt ttgcagctgc cctggatcct cctcttctca
5641 tagcaaaacc caacaaagtc cagcttattg ccatggatct gcccatggtc agtggtgacc
5701 ggatccactg tcttgatatt ttatttgcct ttacaaagcg tgttttgggt gagagtggag
5761 agatggatgc ccttcgaata cagatggaag acaggtttat ggcatcaaac ccctccaaag
5821 tctcttatga gcctattaca accactttga aacgtaaaca agaggaggtg tctgccgcta
5881 tcattcagcg taatttcaga tgttatcttt taaagcaaag gttaaaaaat atatcaagta
5941 actataacaa agaggcaatt aaagggagga ttgacttacc tataaaacaa gacatgatta
6001 ttgacaaact aaatgggaac tccactccag aaaaaacaga tgggagttcc tctaccacct
6061 ctcctccttc ctatgatagt gtaacaaaac cagacaagga aaagtttgag aaagacaaac
6121 cagaaaaaga aagcaaagga aaagaggtca gagaaaatca aaagtaaaaa gaaacaaaga
6181 attatctttg tgatcaattg tttacagcct atgaaggtaa agtatatgtg tcaactggac
6241 ttcaagagga ggtccatgcc aaactgactg ttttaacaaa tactcatagt cagtgcctat
6301 acaagacagt gaagtgacct ctctgtcact gcaactctgt gaagcagggt atcaacattg
6361 acaagaggtt gctgttttta ttaccagctg acactgctga ggagaaaccc aatggctacc

FIGURE 3 (continued)

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6421 tagactatag ggatagttgt gcaaagtgaa cattgtaact acaccaaaca cctttagtac
6481 agtccttgca tccattctat ttttaacttc catatctgcc atatttttac aaaatttgtt
6541 ctagtgcatt tccatggtcc ccaattcata gtttattcat aatgctatgt cactatttt
```

FIGURE 4: amino acid sequence of human SCN3A (SEQ ID NO: 4)

MAQALLVPPGPESFRLFTRESLAAIEKRAAEEKAKKPKKEQDNDDENKPKPNSDLEAGKNLPFI
YGDIPPEMVSEPLEDLDPYYINKKTFIVMNKGKAIFRFSATSALYILTPLNPVRKIAIKILVHS
LFSMLIMCTILTNCVFMTLSNPPDWTKNVEYTFTGIYTFESLIKILARGFCLEDFTFLRDPWNW
LDFSVIVMAYVTEFVSLGNVSALRTFRVLRALKTISVIPGLKTIVGALIQSVKKLSDVMILTVF
CLSVFALIGLQLFMGNLRNKCLQWPPSDSAFETNTTSYFNGTMDSNGTFVNVTMSTFNWKDYIG
DDSHFYVLDGQKDPLLCGNGSDAGQCPEGYICVKAGRNPNYGYTSFDTFSWAFLSLFRLMTQDY
WENLYQLTLRAAGKTYMIFFVLVIFLGSFYLVNLILAVVAMAYEEQNQATLEEAEQKEAEFQQM
LEQLKKQQEEAQAVAAASAASRDFSGIGGLGELLESSSEASKLSSKSAKEWRNRRKKRRQREHL
EGNNKGERDSFPKSESEDSVKRSSFLFSMDGNRLTSDKKFCSPHQSLLSIRGSLFSPRRNSKTS
IFSFRGRAKDVGSENDFADDEHSTFEDSESRRDSLFVPHRHGERRNSNGTTTETEVRKRRLSSY
QISMEMLEDSSGRQRAVSIASILTNTMEELEESRQKCPPCWYRFANVFLIWDCCDAWLKVKHLV
NLIVMDPFVDLAITICIVLNTLFMAMEHYPMTEQFSSVLTVGNLVFTGIFTAEMVLKIIAMDPY
YYFQEGWNIFDGIIVSLSLMELGLSNVEGLSVLRSFRLLRVFKLAKSWPTLNMLIKIIGNSVGA
LGNLTLVLAIIVFIFAVVGMQLFGKSYKECVCKINDDCTLPRWHMNDFFHSFLIVFRVLCGEWI
ETMWDCMEVAGQTMCLIVFMLVMVIGNLVVLNLFLALLLSSFSSDNLAATDDDNEMNNLQIAVG
RMQKGIDYVKNKMRECFQKAFFRKPKVIEIHEGNKIDSCMSNNTGIEISKELNYLRDGNGTTSG
VGTGSSVEKYVIDENDYMSFINNPSLTVTVPIAVGESDFENLNTEEFSSESELEESKEKLNATS
SSEGSTVDVVLPREGEQAETEPEEDLKPEACFTEGCIKKFPFCQVSTEEGKGKIWWNLRKTCYS
IVEHNWFETFIVFMILLSSGALAFEDIYIEQRKTIKTMLEYADKVFTYIFILEMLLKWVAYGFQ
TYFTNAWCWLDFLIVDVSLVSLVANALGYSELGAIKSLRTLRALRPLRALSRFEGMRVVVNALV
GAIPSIMNVLLVCLIFWLIFSIMGVNLFAGKFYHCVNMTTGNMFDISDVNNLSDCQALGKQARW
KNVKVNFDNVGAGYLALLQVATFKGWMDIMYAAVDSRDVKLQPVYEENLYMYLYFVIFIIFGSF
FTLNLFIGVIIDNFNQQKKKFGGQDIFMTEEQKKYYNAMKKLGSKKPQKPIPRPANKFQGMVFD
FVTRQVFDISIMILICLNMVTMMVETDDQGKYMTLVLSRINLVFIVLFTGEFVLKLVSLRHYYF
TIGWNIFDFVVVILSIVGMFLAEMIEKYFVSPTLFRVIRLARIGRILRLIKGAKGIRTLLFALM
MSLPALFNIGLLLFLVMFIYAIFGMSNFAYVKKEAGIDDMFNFETFGNSMICLFQITTSAGWDG
LLAPILNSAPPDCDPDTIHPGSSVKGDCGNPSVGIFFFVSYIIISFLVVVNMYIAVILENFSVA
TEESAEPLSEDDFEMFYEVWEKFDPDATQFIEFSKLSDFAAALDPPLLIAKPNKVQLIAMDLPM
VSGDRIHCLDILFAFTKRVLGESGEMDALRIQMEDRFMASNPSKVSYEPITTTLKRKQEEVSAA
IIQRNFRCYLLKQRLKNISSNYNKEAIKGRIDLPIKQDMIIDKLNGNSTPEKTDGSSSTTSPPS
YDSVTKPDKEKFEKDKPEKESKGKEVRENQK

FIGURE 5: cDNA of human sodium channel a-subunit variant by Jeong et al. (SEQ ID NO: 5)

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   1 agcgaagcgg aggcataagc agagaggatt ctggaaaggt ctctttgttt tcttatccac
  61 agagaaagaa agaaaaaaaa ttgtaactaa tttgtaaacc tctgtggtca aaaaaaaaaa
 121 aaaaaaaaaa gctgaacagc tgccagagga agacacgtta taccctaacc atcttggatg
 181 ctgggctttg ttatgctgta attcataagg ctctgtttta tcagagatta tggagcaaga
 241 aaactgaagc caagccacat caaggtttga cagggatgag atacctgtca aggattcata
 301 gtagagtggc ttactgggaa aggagcaaag aatctcttct agggatattg taagaataaa
 361 tgagataatt cacagaaggg acctggagct tttccggaaa aaggtgctgt gactatctaa
 421 ggtaattcgt atgcaagaag ctacacgtaa ttaaatgtgc aggatgaaaa gatggcacag
 481 gcactgttgg tacccccagg acctgaaagc ttccgccttt ttactagaga atctcttgct
 541 gctatcgaaa aacgtgctgc agaagagaaa gccaagaagc ccaaaaagga acaagataat
 601 gatgatgaga acaaaccaaa gccaaatagt gacttggaag ctggaaagaa ccttccattt
 661 atttatggag acattcctcc agagatggtg tcagagcccc tggaggacct ggatccctac
 721 tatatcaata agaaaacttt tatagtaatg aataaaggaa aggcaatttt ccgattcagt
 781 gccacctctg ccttgtatat tttaactcca ctaaaccctg ttaggaaaat tgctatcaag
 841 attttggtac attctttatt cagcatgctt atcatgtgca ctattttgac caactgtgta
 901 tttatgacct tgagcaaccc tcctgactgg acaaagaatg tagagtacac attcactgga
 961 atctatacct ttgagtcact tataaaaatc ttggcaagag ggttttgctt agaagatttt
1021 acgtttcttc gtgatccatg gaactggctg gatttcagtg tcattgtgat ggcatatgtg
1081 acagagtttg tggacctggg caatgtctca gcgttgagaa cattcagagt tctccgagca
1141 ctgaaaacaa tttcagtcat tccaggttta aagaccattg tgggggccct gatccagtcg
1201 gtaaagaagc tttctgatgt gatgatcctg actgtgttct gtctgagcgt gtttgctctc
1261 attgggctgc agctgttcat gggcaatctg aggaataaat gtttgcagtg gcccccaagc
1321 gattctgctt ttgaaaccaa caccacttcc tactttaatg gcacaatgga ttcaaatggg
1381 acatttgtta atgtaacaat gagcacattt aactggaagg attacattgg agatgacagt
1441 cacttttatg ttttggatgg gcaaaaagac cctttactct gtggaaatgg ctcagatgca
1501 ggccagtgtc cagaaggata catctgtgtg aaggctggtc gaaaccccaa ctatggctac
1561 acaagctttg acacctttag ctgggctttc ctgtctctat ttcgactcat gactcaagac
1621 tattgggaaa atctttacca gttgacatta cgtgctgctg ggaaaacata catgatattt
1681 tttgtcctgg tcatttttctt gggctcattt tatttggtga atttgatcct ggctgtggtg
1741 gccatggcct atgaggagca gaatcaggcc accttggaag aagcagaaca aaaagaggcc
1801 gaatttcagc agatgctcga acagcttaaa aagcaacagg aagaagctca ggcagttgcg
1861 gcagcatcag ctgcttcaag agatttcagt ggagtaggtg ggttaggaga gctgttggaa
1921 agttcttcag aagcatcaaa gttgagttcc aaaggtgcta aagaatggag gaaccggagg
1981 aagaaaagaa gacagagaga gcaccttgaa ggaaacaaca aaggagagag agacagcttt
2041 cccaaatccg aatctgaaga cagcgtcaaa agaagcagct tccttttctc catggatgga
2101 aacagactga ccagtgacaa aaaattctgc tcccctcatc agtctctctt gagtatccgt
2161 ggctccctgt tttccccaag acgcaatagc aaaacaagca ttttcagttt cagaggtcgg
2221 gcaaaggatg ttggatctga aaatgacttt gctgatgatg aacacagcac atttgaagac
2281 ggcgaaagca ggagagactc actgtttgtg ccgcacagac atggagagcg acgcaacagt
2341 aacgttagtc aggccagtat gtcatccagg atggtgccag ggcttccagc aaatgggaag
2401 atgcacagca ctgtggattg caatggtgtg gtttccttgg tgggtggacc ttcagctcta
2461 acgtcaccta ctggacaact tcccccagag ggcaccacca ctgaaacgga agtcagaaag
2521 agaaggttaa gctcttacca gatttcaatg gagatgctgg aggattcctc tggaaggcaa
2581 agagccgtga gcatagccag cattctgacc aacacaatgg aagaacttga agaatctaga
2641 cagaaatgtc cgccatgctg gtatagattt gccaatgtgt tcttgatctg ggactgctgt
2701 gatgcatggt taaaagtaaa acatcttgtg aatttaattg ttatggatcc atttgttgat
2761 cttgccatca ctatttgcat tgtcttaaat accctcttta tggccatgga gcactacccc
2821 atgactgagc aattcagtag tgtgttgact gtaggaaacc tggtctttac tgggattttc
2881 acagcagaaa tggttctcaa gatcattgcc atggatcctt attactattt ccaagaaggc
2941 tggaatatct ttgatggaat tattgtcagc ctcagtttaa tggagcttgg tctgtcaaat
3001 gtggagggat tgtctgtact gcgatcattc agactgctta gagttttcaa gttggcaaaa
3061 tcctggccca cactaaatat gctaattaag atcattggca attctgtggg ggctctagga
3121 aacctcacct tggtgttggc catcatcgtc ttcatttttg ctgtggtcgg catgcagctc
```

FIGURE 5 (continued)

```
3181 tttggtaaga gctacaaaga atgtgtctgc aagatcaatg atgactgtac gctcccacgg
3241 tggcacatga acgacttctt ccactccttc ctgattgtgt tccgcgtgct gtgtggagag
3301 tggatagaga ccatgtggga ctgtatggag gtcgctggcc aaaccatgtg ccttattgtt
3361 ttcatgttgg tcatggtcat tggaaacctt gtggttctga acctctttct ggccttatta
3421 ttgagttcat ttagctcaga caaccttgct gctactgatg atgacaatga aatgaataat
3481 ctgcagattg cagtaggaag aatgcaaaag ggaattgatt atgtgaaaaa taagatgcgg
3541 gagtgtttcc aaaaagcctt ttttagaaag ccaaaagtta tagaaatcca tgaaggcaat
3601 aagatagaca gctgcatgtc caataatact ggaattgaaa taagcaaaga gcttaattat
3661 cttagagatg ggaatggaac caccagtggt gtaggtactg gaagcagtgt tgaaaaatac
3721 gtaatcgatg aaaatgatta tatgtcattc ataaacaacc ccagcctcac cgtcacagtg
3781 ccaattgctg ttggagagtc tgactttgaa aacttaaata ctgaagagtt cagcagtgag
3841 tcagaactag aagaaagcaa agagaaatta aatgcaacca gctcatctga aggaagcaca
3901 gttgatgttg ttctaccccg agaaggtgaa caagctgaaa ctgaacccga agaagacttt
3961 aaaccggaag cttgttttac tgaagggtgt attaaaaagt ttccattctg tcaagtaagt
4021 acagaagaag gcaaagggaa gatctggtgg aatcttcgaa aaacctgcta cagtattgtt
4081 gagcacaact ggtttgagac tttcattgtg ttcatgatcc ttctcagtag tggtgcattg
4141 gcctttgaag atatatacat tgaacagcga aagactatca aaaccatgct agaatatgct
4201 gacaaagtct ttacctatat attcattctg gaaatgcttc tcaaatgggt tgcttatgga
4261 tttcaaacat atttcactaa tgcctggtgc tggctagatt tcttgatcgt tgatgtttct
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4441 gttgtgaatg ctcttgttgg agcaattccc tctatcatga atgtgctgtt ggtctgtctc
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4561 tgtgttaaca tgacaacggg taacatgttt gacattagtg atgttaacaa tttgagtgac
4621 tgtcaggctc ttggcaagca agctcggtgg aaaaacgtga aagtaaactt tgataatgtt
4681 ggcgctggct atcttgcact gcttcaagtg gccacattta aaggctggat ggatattatg
4741 tatgcagctg ttgattcacg agatgttaaa cttcagcctg tatatgaaga aaatctgtac
4801 atgtatttat actttgtcat ctttatcatc tttgggtcat tcttcactct gaatctattc
4861 attggtgtca tcatagataa cttcaaccag cagaaaaaga agtttggagg tcaagacatc
4921 tttatgacag aggaacagaa aaaatattac aatgcaatga agaaacttgg atccaagaaa
4981 cctcagaaac ccatacctcg cccagcaaac aaattccaag gaatggtctt tgattttgta
5041 accagacaag tctttgatat cagcatcatg atcctcatct gcctcaacat ggtcaccatg
5101 atggtggaaa cggatgacca gggcaaatac atgaccctag ttttgtcccg gatcaaccta
5161 gtgttcattg ttctgttcac tggagaattt gtgctgaagc tcgtttccct cagacactac
5221 tacttcacta taggctggaa catctttgac tttgtggtgg tgattctctc cattgtaggt
5281 atgtttctgg ctgagatgat agaaaagtat tctgtgtccc ctaccttgtt ccgagtgatc
5341 cgtcttgcca ggattggccg aatcctacgt ctgatcaaag gagcaaaggg gatccgcacg
5401 ctgctctttg ctttgatgat gtcccttcct gcgttgttta acatcggcct cctgctcttc
5461 ctggtcatgt ttatctatgc catctttggg atgtccaact ttgcctatgt taaaaaggaa
5521 gctggaattg atgacatgtt caactttgag acctttggca acagcatgat ctgcttgttc
5581 caaattacaa cctctgctgg ctgggatgga ttgctagcac ctattcttaa tagtgcacca
5641 cccgactgtg accctgacac aattcaccct ggcagctcag ttaagggaga ccgtggggac
5701 ccatctgttg ggattttctt ttttgtcagt tacatcatca tatccttcct ggttgtggtg
5761 aacatgtaca tcgcggtcat cctggagaac ttcagtgttg ctactgaaga aagtgcagag
5821 cccctgagtg aggatgactt tgagatgttc tatgaggttt gggaaaagtt tgatcccgat
5881 gcgacccagt ttatagagtt ctctaaactc tctgattttg cagctgccct ggatcctcct
5941 cttctcatag caaaacccaa caaagtccag cttattgcca tggatctgcc catggtcagt
6001 ggtgaccgga tccactgtct tgatatttta tttgccttta caaagcgtgt tttgtgtgag
6061 agtggagaga tggatgccct tcgaatacag atggaagaca ggtttatggc atcaaacccc
6121 tccaaagtct cttatgagcc tattacaacc actttgaaac gtaaacaaga ggaggtgtct
6181 gccgctatca ttcagcgtaa tttcagatgt tatcttttaa agcaaaggtt aaaaaatata
6241 tcaagtaact ataacaaaga ggcaattaaa gggaggattg acttacctat aaaacaagac
6301 atgattattg acaaactaaa tgggaactcc actccagaaa aaacagatgg gagttcctct
6361 accacccctc ctccttccta tgatagtgta acaaaaccag acaaggaaaa gtttgagaaa
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FIGURE 5 (continued)

6421 gacaaaccag aaaaagaaag caaaggaaaa gaggtcagag aaaatcaaaa gtaaaaagaa
6481 acaaagaatt atctttgtga tcaattgttt acagcctatg aaggtaaagt atatgtgtca
6541 actggacttc aagaggaggt ccatgccaaa ctgactgttt taacaaatac tcatagtcag
6601 tgcctataca agacagtgaa gtgacctctc tgtcactgca actctgtgaa gcagggtatc
6661 aacgttgaca agaggttgct gtttttatta ccagctgaca ctgctgagga gaaacccaat
6721 ggctacctag actataggga tagttgtgca aagtgaacat tgtaactaca ccaaacacct
6781 ttagtacagt ccttgcatcc attctatttt taacttccat atctgccata tttttacaaa
6841 atttgttcta gtgcatttcc atggtcccca attcatagtt tattcataat gctatgtcac
6901 tatttttgta aatgaggttt acgttgaaga aacagtatac aagaaccctg tctctcaaat
6961 gatcagacaa aggtgttttg ccagagagat aaaatttttg ctcaaaacca gaaaaagaat
7021 tgtaatggct acagtttcag ttacttccat tttctagatg gctttaattt tgaaagtatt
7081 ttagtctgtt atgtttgttt ctatctgaac agttatgtgc ctgtaaagtc tcctctaata
7141 tttaaaggat tatttttatg caaagtattc tgtttcagca agtgcaaatt ttattctaag
7201 tttcagagct ctatatttaa tttaggtcaa atgctttcca aaaagtaatc taataaatcc
7261 attctagaaa aatatatcta aagtattgct ttagaatagt tgttccactt tctgctgcag
7321 tattgctttg ccatcttctg ctctcagcaa agctgatagt ctatgtcaat taaataccct
7381 atgttatgta aatagttatt ttatcctgtg gtgcatgttt gggcaaatat atatatagcc
7441 tgataaacaa cttctattaa atcaaatatg taccacagtg tatgtgtctt ttgcaagctt
7501 ccaacaggga tgtatcctgt atcattcatt aaacatagtt taaaggctat cactaatgca
7561 tgttaatatt gcctatgctg ctctatttta ctcaatccat tcttcacaag tcttggttaa
7621 agaatgtcac atattggtga tagaatgaat tcaacctgct ctgtccatta tgtcaagcag
7681 aataatttga agctatttac aaacaccttt acttttgcac ttttaattca acatgagtat
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7861 tataatcaac tttatttgtc agcattttgt acataagaaa attattttca ggttgatgac
7921 atcacaattt attttacttt atgcttttgc ttttgatttt taatcacaat tccaaacttt
7981 tgaatccata agatttttca atggataatt tcctaaaata aaagttagat aatgggtttt
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8101 actcaaacct agatcatttt ctaccaacta tggttgcctc aatataacct tttattcata
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8341 accaaaagtt taatgttaat tctttttaca aaactattta ctgtagtgta ttgaagaact
8401 gcatgcaggg aattgctatt gctaaaaaga atggtgagct acgtcattat tgagccaaaa
8461 gaataaattt catttttat tgcatttcac ttattgggct ctggggtttt ttgtttttgt
8521 tttttgctgt tggcagttta aaatatatat aattaataaa acctgtgctt gatctgacat
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8641 tactacagaa caaaggcaaa ttaaaagcag ctttgtgaac ttttatgtgt gcaaaggatc
8701 aagttcacat gttccaactt tcaggtttga taataatagt agtaaccacc tacaatagct
8761 ttcaatttca attaactccc ttggctataa gcatctaaac tcatcttctt tcaatataat
8821 tgatgctatc tcctaattac ttggtggcta ataaatgtta cattctttgt tacttaaatg
8881 cattatataa actcctatgt atacataagg tattaatgat atagttattg agaatttata
8941 ttaacttttt tttcaagaac ccttggattt atgtgaggtc aaaaccaaac tcttattctc
9001 agtggaaaac tccagttgta atgcatattt ttaaagacaa tttggatcta aatatgtatt
9061 tcataattct cccataataa attatataag gtggaaaaaa aaaaaaaaaa aaaaaaaaaa
9121 aaa

FIGURE 6: amino acid sequence of human sodium channel α-subunit variant by Jeong et al. (SEQ ID NO: 6)

MAQALLVPPGPESFRLFTRESLAAIEKRAAEEKAKKPKKEQDNDDENKPKPNSDLEAGKNLPFI
YGDIPPEMVSEPLEDLDPYYINKKTFIVMNKGKAIFRFSATSALYILTPLNPVRKIAIKILVHS
LFSMLIMCTILTNCVFMTLSNPPDWTKNVEYTFTGIYTFESLIKILARGFCLEDFTFLRDPWNW
LDFSVIVMAYVTEFVDLGNVSALRTFRVLRALKTISVIPGLKTIVGALIQSVKKLSDVMILTVF
CLSVFALIGLQLFMGNLRNKCLQWPPSDSAFETNTTSYFNGTMDSNGTFVNVTMSTFNWKDYIG
DDSHFYVLDGQKDPLLCGNGSDAGQCPEGYICVKAGRNPNYGYTSFDTFSWAFLSLFRLMTQDY
WENLYQLTLRAAGKTYMIFFVLVIFLGSFYLVNLILAVVAMAYEEQNQATLEEAEQKEAEFQQM
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NGKMHSTVDCNGVVSLVGGPSALTSPTGQLPPEGTTTETEVRKRRLSSYQISMEMLEDSSGRQR
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CFQKAFFRKPKVIEIHEGNKIDSCMSNNTGIEISKELNYLRDGNGTTSGVGTGSSVEKYVIDEN
DYMSFINNPSLTVTVPIAVGESDFENLNTEEFSSESELEESKEKLNATSSSEGSTVDVVLPREG
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DVSLVSLVANALGYSELGAIKSLRTLRALRPLRALSRFEGMRVVVNALVGAIPSIMNVLLVCLI
FWLIFSIMGVNLFAGKFYHCVNMTTGNMFDISDVNNLSDCQALGKQARWKNVKVNFDNVGAGYL
ALLQVATFKGWMDIMYAAVDSRDVKLQPVYEENLYMYLYFVIFIIFGSFFTLNLFIGVIIDNFN
QQKKKFGGQDIFMTEEQKKYYNAMKKLGSKKPQKPIPRPANKFQGMVFDFVTRQVFDISIMILI
CLNMVTMMVETDDQGKYMTLVLSRINLVFIVLFTGEFVLKLVSLRHYYFTIGWNIFDFVVVILS
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VMFIYAIFGMSNFAYVKKEAGIDDMFNFETFGNSMICLFQITTSAGWDGLLAPILNSAPPDCDP
DTIHPGSSVKGDRGDPSVGIFFFVSYIIISFLVVVNMYIAVILENFSVATEESAEPLSEDDFEM
FYEVWEKFDPDATQFIEFSKLSDFAAALDPPLLIAKPNKVQLIAMDLPMVSGDRIHCLDILFAF
TKRVLGESGEMDALRIQMEDRFMASNPSKVSYEPITTTLKRKQEEVSAAIIQRNFRCYLLKQRL
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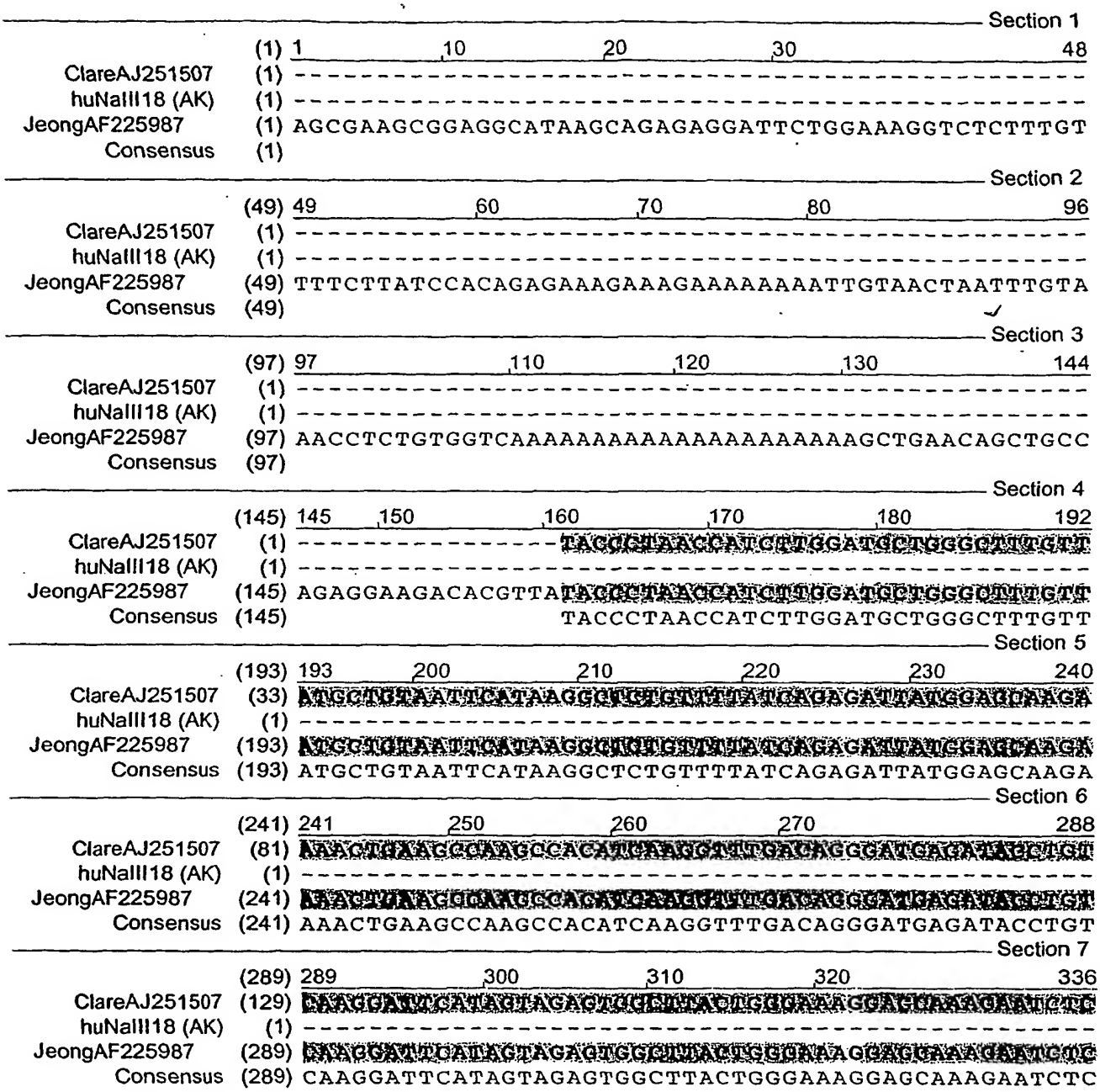
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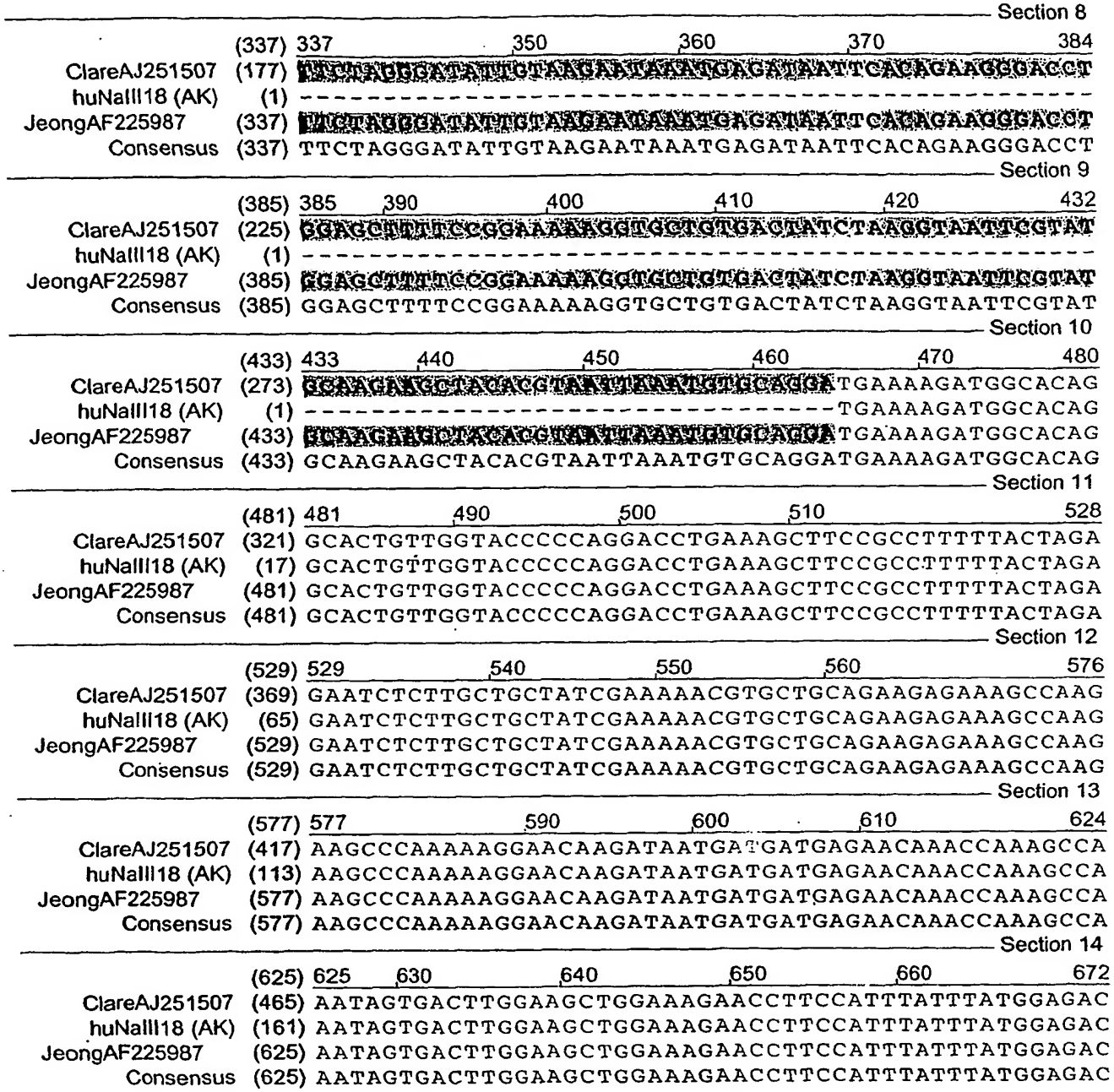
(1) 1 10 20 30 48
ClareAJ251507 (1) ----------
huNalII18 (AK) (1) ----------
JeongAF225987 (1) AGCGAAGCGGAGGCATAAGCAGAGAGGATTCTGGAAAGGTCTCTTTGT
Consensus (1)
Section 2
(49) 49 60 70 80 96
ClareAJ251507 (1) ----------
huNalII18 (AK) (1) ----------
JeongAF225987 (49) TTTCTTATCCACAGAGAAAGAAAGAAAAAAAATTGTAACTAATTTGTA
Consensus (49)
Section 3
(97) 97 110 120 130 144
ClareAJ251507 (1) ----------
huNalII18 (AK) (1) ----------
JeongAF225987 (97) AACCTCTGTGGTCAAAAAAAAAAAAAAAAAAAAAAGCTGAACAGCTGCC
Consensus (97)
Section 4
(145) 145 150 160 170 180 192
ClareAJ251507 (1) ----------
huNalII18 (AK) (1) ----------
JeongAF225987 (145) AGAGGAAGACACGTTA
Consensus (145) TACCCTAACCATCTTGGATGCTGGGCTTTGTT
Section 5
(193) 193 200 210 220 230 240
ClareAJ251507 (33)
huNalII18 (AK) (1) ----------
JeongAF225987 (193)
Consensus (193) ATGCTGTAATTCATAAGGCTCTGTTTTATCAGAGATTATGGAGCAAGA
Section 6
(241) 241 250 260 270 288
ClareAJ251507 (81)
huNalII18 (AK) (1) ----------
JeongAF225987 (241)
Consensus (241) AAACTGAAGCCAAGCCACATCAAGGTTTGACAGGGATGAGATACCTGT
Section 7
(289) 289 300 310 320 336
ClareAJ251507 (129)
huNalII18 (AK) (1) ----------
JeongAF225987 (289)
Consensus (289) CAAGGATTCATAGTAGAGTGGCTTACTGGGAAAGGAGCAAAGAATCTC


Section 8
(337) 337 350 360 370 384
ClareAJ251507 (177) TTCTAGGGATATTGTAAGAATAAATGAGATAATTCACAGAAGGGACCT
huNalII18 (AK) (1) ----------
JeongAF225987 (337) TTCTAGGGATATTGTAAGAATAAATGAGATAATTCACAGAAGGGACCT
Consensus (337) TTCTAGGGATATTGTAAGAATAAATGAGATAATTCACAGAAGGGACCT
Section 9
(385) 385 390 400 410 420 432
ClareAJ251507 (225) GGAGCTTTTCCGGAAAAAGGTGCTGTGACTATCTAAGGTAATTCGTAT
huNalII18 (AK) (1) ----------
JeongAF225987 (385) GGAGCTTTTCCGGAAAAAGGTGCTGTGACTATCTAAGGTAATTCGTAT
Consensus (385) GGAGCTTTTCCGGAAAAAGGTGCTGTGACTATCTAAGGTAATTCGTAT
Section 10
(433) 433 440 450 460 470 480
ClareAJ251507 (273) GCAAGAAGCTACACGTAATTAAATGTGCAGGATGAAAAGATGGCACAG
huNalII18 (AK) (1) ----------TGAAAAGATGGCACAG
JeongAF225987 (433) GCAAGAAGCTACACGTAATTAAATGTGCAGGATGAAAAGATGGCACAG
Consensus (433) GCAAGAAGCTACACGTAATTAAATGTGCAGGATGAAAAGATGGCACAG
Section 11
(481) 481 490 500 510 528
ClareAJ251507 (321) GCACTGTTGGTACCCCCAGGACCTGAAAGCTTCCGCCTTTTTACTAGA
huNalII18 (AK) (17) GCACTGTTGGTACCCCCAGGACCTGAAAGCTTCCGCCTTTTTACTAGA
JeongAF225987 (481) GCACTGTTGGTACCCCCAGGACCTGAAAGCTTCCGCCTTTTTACTAGA
Consensus (481) GCACTGTTGGTACCCCCAGGACCTGAAAGCTTCCGCCTTTTTACTAGA
Section 12
(529) 529 540 550 560 576
ClareAJ251507 (369) GAATCTCTTGCTGCTATCGAAAAACGTGCTGCAGAAGAGAAAGCCAAG
huNalII18 (AK) (65) GAATCTCTTGCTGCTATCGAAAAACGTGCTGCAGAAGAGAAAGCCAAG
JeongAF225987 (529) GAATCTCTTGCTGCTATCGAAAAACGTGCTGCAGAAGAGAAAGCCAAG
Consensus (529) GAATCTCTTGCTGCTATCGAAAAACGTGCTGCAGAAGAGAAAGCCAAG
Section 13
(577) 577 590 600 610 624
ClareAJ251507 (417) AAGCCCAAAAAGGAACAAGATAATGATGATGAGAACAAACCAAAGCCA
huNalII18 (AK) (113) AAGCCCAAAAAGGAACAAGATAATGATGATGAGAACAAACCAAAGCCA
JeongAF225987 (577) AAGCCCAAAAAGGAACAAGATAATGATGATGAGAACAAACCAAAGCCA
Consensus (577) AAGCCCAAAAAGGAACAAGATAATGATGATGAGAACAAACCAAAGCCA
Section 14
(625) 625 630 640 650 660 672
ClareAJ251507 (465) AATAGTGACTTGGAAGCTGGAAAGAACCTTCCATTTATTTATGGAGAC
huNalII18 (AK) (161) AATAGTGACTTGGAAGCTGGAAAGAACCTTCCATTTATTTATGGAGAC
JeongAF225987 (625) AATAGTGACTTGGAAGCTGGAAAGAACCTTCCATTTATTTATGGAGAC
Consensus (625) AATAGTGACTTGGAAGCTGGAAAGAACCTTCCATTTATTTATGGAGAC

Section 15

	(673)	673 680 690 700 710 720
ClareAJ251507	(513)	ATTCCTCCAGAGATGGTGTCAGAGCCCCTGGAGGACCTGGATCCCTAC
huNaIII18 (AK)	(209)	ATTCCTCCAGAGATGGTGTCAGAGCCCCTGGAGGACCTGGATCCCTAC
JeongAF225987	(673)	ATTCCTCCAGAGATGGTGTCAGAGCCCCTGGAGGACCTGGATCCCTAC
Consensus	(673)	ATTCCTCCAGAGATGGTGTCAGAGCCCCTGGAGGACCTGGATCCCTAC

Section 16

	(721)	721 730 740 750 768
ClareAJ251507	(561)	TATATCAATAAGAAAACTTTTATAGTAATGAATAAAGGAAAGGCAATT
huNaIII18 (AK)	(257)	TATATCAATAAGAAAACTTTTATAGTAATGAATAAAGGAAAGGCAATT
JeongAF225987	(721)	TATATCAATAAGAAAACTTTTATAGTAATGAATAAAGGAAAGGCAATT
Consensus	(721)	TATATCAATAAGAAAACTTTTATAGTAATGAATAAAGGAAAGGCAATT

Section 17

	(769)	769 780 790 800 816
ClareAJ251507	(609)	TTCCGATTCAGTGCCACCTCTGCCTTGTATATTTTAACTCCACTAAAC
huNaIII18 (AK)	(305)	TTCCGATTCAGTGCCACCTCTGCCTTGTATATTTTAACTCCACTAAAC
JeongAF225987	(769)	TTCCGATTCAGTGCCACCTCTGCCTTGTATATTTTAACTCCACTAAAC
Consensus	(769)	TTCCGATTCAGTGCCACCTCTGCCTTGTATATTTTAACTCCACTAAAC

Section 18

	(817)	817 830 840 850 864
ClareAJ251507	(657)	CCTGTTAGGAAAATTGCTATCAAGATTTTGGTACATTCTTTATTCAGC
huNaIII18 (AK)	(353)	CCTGTTAGGAAAATTGCTATCAAGATTTTGGTACATTCTTTATTCAGC
JeongAF225987	(817)	CCTGTTAGGAAAATTGCTATCAAGATTTTGGTACATTCTTTATTCAGC
Consensus	(817)	CCTGTTAGGAAAATTGCTATCAAGATTTTGGTACATTCTTTATTCAGC

Section 19

	(865)	865 870 880 890 900 912
ClareAJ251507	(705)	ATGCTTATCATGTGCACTATTTTGACCAACTGTGTATTTATGACCTTG
huNaIII18 (AK)	(401)	ATGCTTATCATGTGCACTATTTTGACCAACTGTGTATTTATGACCTTG
JeongAF225987	(865)	ATGCTTATCATGTGCACTATTTTGACCAACTGTGTATTTATGACCTTG
Consensus	(865)	ATGCTTATCATGTGCACTATTTTGACCAACTGTGTATTTATGACCTTG

Section 20

	(913)	913 920 930 940 950 960
ClareAJ251507	(753)	AGCAACCCTCCTGACTGGACAAAGAATGTAGAGTACACATTCACTGGA
huNaIII18 (AK)	(449)	AGCAACCCTCCTGACTGGACAAAGAATGTAGAGTACACATTCACTGGA
JeongAF225987	(913)	AGCAACCCTCCTGACTGGACAAAGAATGTAGAGTACACATTCACTGGA
Consensus	(913)	AGCAACCCTCCTGACTGGACAAAGAATGTAGAGTACACATTCACTGGA

Section 21

	(961)	961 970 980 990 1008
ClareAJ251507	(801)	ATCTATACCTTTGAGTCACTTATAAAAATCTTGGCAAGAGGGTTTTGC
huNaIII18 (AK)	(497)	ATCTATACCTTTGAGTCACTTATAAAAATCTTGGCAAGAGGGTTTTGC
JeongAF225987	(961)	ATCTATACCTTTGAGTCACTTATAAAAATCTTGGCAAGAGGGTTTTGC
Consensus	(961)	ATCTATACCTTTGAGTCACTTATAAAAATCTTGGCAAGAGGGTTTTGC

Section 22

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                (1009) 1009          1020          1030          1040          1056
ClareAJ251507   (849) TTAGAAGATTTTACGTTTCTTCGTGATCCATGGAACTGGCTGGATTTC
huNaIII18 (AK)  (545) TTAGAAGATTTTACGTTTCTTCGTGATCCATGGAACTGGCTGGATTTC
JeongAF225987   (1009) TTAGAAGATTTTACGTTTCTTCGTGATCCATGGAACTGGCTGGATTTC
Consensus       (1009) TTAGAAGATTTTACGTTTCTTCGTGATCCATGGAACTGGCTGGATTTC
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Section 23

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                (1057) 1057          1070          1080          1090          1104
ClareAJ251507   (897) AGTGTCATTGTGATGGCGTATGTAACAGAATTTGTAAGCCTAGGCAAT
huNaIII18 (AK)  (593) AGTGTCATTGTGATGGCGTATGTAACAGAATTTGTAAGCCTAGGCAAT
JeongAF225987   (1057) AGTGTCATTGTGATGGCATATGTGACAGAGTTTGTGGACCTGGGCAAT
Consensus       (1057) AGTGTCATTGTGATGGCGTATGTAACAGAATTTGTAAGCCTAGGCAAT
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Section 24

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                (1105) 1105  1110          1120          1130          1140          1152
ClareAJ251507   (945) GTTTCAGCCCTTCGAACTTTCAGAGTCTTGAGAGCTCTGAAAACTATT
huNaIII18 (AK)  (641) GTTTCAGCCCTTCGAACTTTCAGAGTCTTGAGAGCTCTGAAAACTATT
JeongAF225987   (1105) GTCTCAGCGTTGAGAACATTCAGAGTTCTCCGAGCACTGAAAACAATT
Consensus       (1105) GTTTCAGCCCTTCGAACTTTCAGAGTCTTGAGAGCTCTGAAAACTATT
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Section 25

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                (1153) 1153          1160          1170          1180          1190          1200
ClareAJ251507   (993) TCTGTAATTCCAGGTTTAAAGACCATTGTGGGGGCCCTGATCCAGTCG
huNaIII18 (AK)  (689) TCTGTAATTCCAGGTTTAAAGACCATTGTGGGGGCCCTGATCCAGTCG
JeongAF225987   (1153) TCAGTCATTCCAGGTTTAAAGACCATTGTGGGGGCCCTGATCCAGTCG
Consensus       (1153) TCTGTAATTCCAGGTTTAAAGACCATTGTGGGGGCCCTGATCCAGTCG
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Section 26

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                (1201) 1201          1210          1220          1230          1248
ClareAJ251507   (1041) GTAAAGAAGCTTTCTGATGTGATGATCCTGACTGTGTTCTGTCTGAGC
huNaIII18 (AK)  (737) GTAAAGAAGCTTTCTGATGTGATGATCCTGACTGTGTTCTGTCTGAGC
JeongAF225987   (1201) GTAAAGAAGCTTTCTGATGTGATGATCCTGACTGTGTTCTGTCTGAGC
Consensus       (1201) GTAAAGAAGCTTTCTGATGTGATGATCCTGACTGTGTTCTGTCTGAGC
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Section 27

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                (1249) 1249          1260          1270          1280          1296
ClareAJ251507   (1089) GTGTTTGCTCTCATTGGGCTGCAGCTGTTCATGGGCAATCTGAGGAAT
huNaIII18 (AK)  (785) GTGTTTGCTCTCATTGGGCTGCAGCTGTTCATGGGCAATCTGAGGAAT
JeongAF225987   (1249) GTGTTTGCTCTCATTGGGCTGCAGCTGTTCATGGGCAATCTGAGGAAT
Consensus       (1249) GTGTTTGCTCTCATTGGGCTGCAGCTGTTCATGGGCAATCTGAGGAAT
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Section 28

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                (1297) 1297          1310          1320          1330          1344
ClareAJ251507   (1137) AAATGTTTGCAGTGGCCCCCAAGCGATTCTGCTTTTGAAACCAACACC
huNaIII18 (AK)  (833) AAATGTTTGCAGTGGCCCCCAAGCGATTCTGCTTTTGAAACCAACACC
JeongAF225987   (1297) AAATGTTTGCAGTGGCCCCCAAGCGATTCTGCTTTTGAAACCAACACC
Consensus       (1297) AAATGTTTGCAGTGGCCCCCAAGCGATTCTGCTTTTGAAACCAACACC
```

Section 29

	(1345)	1345 1350 1360 1370 1380 1392
ClareAJ251507	(1185)	ACTTCCTACTTTAATGGCACAATGGATTCAAATGGGACATTTGTTAAT
huNalII18 (AK)	(881)	ACTTCCTACTTTAATGGCACAATGGATTCAAATGGGACATTTGTTAAT
JeongAF225987	(1345)	ACTTCCTACTTTAATGGCACAATGGATTCAAATGGGACATTTGTTAAT
Consensus	(1345)	ACTTCCTACTTTAATGGCACAATGGATTCAAATGGGACATTTGTTAAT

Section 30

	(1393)	1393 1400 1410 1420 1430 1440
ClareAJ251507	(1233)	GTAACAATGAGCACATTTAACTGGAAGGATTACATTGGAGATGACAGT
huNalII18 (AK)	(929)	GTAACAATGAGCACATTTAACTGGAAGGATTACATTGGAGATGACAGT
JeongAF225987	(1393)	GTAACAATGAGCACATTTAACTGGAAGGATTACATTGGAGATGACAGT
Consensus	(1393)	GTAACAATGAGCACATTTAACTGGAAGGATTACATTGGAGATGACAGT

Section 31

	(1441)	1441 1450 1460 1470 1488
ClareAJ251507	(1281)	CACTTTTATGTTTTGGATGGGCAAAAAGACCCTTTACTCTGTGGAAAT
huNalII18 (AK)	(977)	CACTTTTATGTTTTGGATGGGCAAAAAGACCCTTTACTCTGTGGAAAT
JeongAF225987	(1441)	CACTTTTATGTTTTGGATGGGCAAAAAGACCCTTTACTCTGTGGAAAT
Consensus	(1441)	CACTTTTATGTTTTGGATGGGCAAAAAGACCCTTTACTCTGTGGAAAT

Section 32

	(1489)	1489 1500 1510 1520 1536
ClareAJ251507	(1329)	GGCTCAGATGCAGGCCAGTGTCCAGAAGGATACATCTGTGTGAAGGCT
huNalII18 (AK)	(1025)	GGCTCAGATGCAGGCCAGTGTCCAGAAGGATACATCTGTGTGAAGGCT
JeongAF225987	(1489)	GGCTCAGATGCAGGCCAGTGTCCAGAAGGATACATCTGTGTGAAGGCT
Consensus	(1489)	GGCTCAGATGCAGGCCAGTGTCCAGAAGGATACATCTGTGTGAAGGCT

Section 33

	(1537)	1537 1550 1560 1570 1584
ClareAJ251507	(1377)	GGTCGAAACCCCAACTATGGCTACACAAGCTTTGACACCTTTAGCTGG
huNalII18 (AK)	(1073)	GGTCGAAACCCCAACTATGGCTACACAAGCTTTGACACCTTTAGCTGG
JeongAF225987	(1537)	GGTCGAAACCCCAACTATGGCTACACAAGCTTTGACACCTTTAGCTGG
Consensus	(1537)	GGTCGAAACCCCAACTATGGCTACACAAGCTTTGACACCTTTAGCTGG

Section 34

	(1585)	1585 1590 1600 1610 1620 1632
ClareAJ251507	(1425)	GCTTTCCTGTCTCTATTTCGACTCATGACTCAAGA[G]TA[G]TGGGAAAAT
huNalII18 (AK)	(1121)	GCTTTCCTGTCTCTATTTCGACTCATGACTCAAGATTA[G]TGGGAAAAT
JeongAF225987	(1585)	GCTTTCCTGTCTCTATTTCGACTCATGACTCAAGA[G]TATTGGGAAAAT
Consensus	(1585)	GCTTTCCTGTCTCTATTTCGACTCATGACTCAAGACTACTGGGAAAAT

Section 35

	(1633)	1633 1640 1650 1660 1670 1680
ClareAJ251507	(1473)	CTTTACCAGTTGACATTACGTGCTGCTGGGAAAACATACATGATATTT
huNalII18 (AK)	(1169)	CTTTACCAGTTGACATTACGTGCTGCTGGGAAAACATACATGATATTT
JeongAF225987	(1633)	CTTTACCAGTTGACATTACGTGCTGCTGGGAAAACATACATGATATTT
Consensus	(1633)	CTTTACCAGTTGACATTACGTGCTGCTGGGAAAACATACATGATATTT

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                                                                 Section 36
                 (1681) 1681      1690      1700      1710             1728
ClareAJ251507    (1521) TTTGTCCTGGTCATTTTCTTGGGCTCATTTTATTTGGTGAATTTGATC
huNaIII18 (AK)   (1217) TTTGTCCTGGTCATTTTCTTGGGCTCATTTTATTTGGTGAATTTGATC
JeongAF225987    (1681) TTTGTCCTGGTCATTTTCTTGGGCTCATTTTATTTGGTGAATTTGATC
Consensus        (1681) TTTGTCCTGGTCATTTTCTTGGGCTCATTTTATTTGGTGAATTTGATC
                                                                 Section 37
                 (1729) 1729      1740      1750      1760             1776
ClareAJ251507    (1569) CTGGCTGTGGTGGCCATGGCCTATGAGGAGCAGAATCAGGCCACCTTG
huNaIII18 (AK)   (1265) CTGGCTGTGGTGGCCATGGCCTATGAGGAGCAGAATCAGGCCACCTTG
JeongAF225987    (1729) CTGGCTGTGGTGGCCATGGCCTATGAGGAGCAGAATCAGGCCACCTTG
Consensus        (1729) CTGGCTGTGGTGGCCATGGCCTATGAGGAGCAGAATCAGGCCACCTTG
                                                                 Section 38
                 (1777) 1777         1790      1800      1810          1824
ClareAJ251507    (1617) GAAGAAGCAGAACAAAAAGAGGCCGAATTTCAGCAGATGCTCGAACAG
huNaIII18 (AK)   (1313) GAAGAAGCAGAACAAAAAGAGGCCGAATTTCAGCAGATGCTCGAACAG
JeongAF225987    (1777) GAAGAAGCAGAACAAAAAGAGGCCGAATTTCAGCAGATGCTCGAACAG
Consensus        (1777) GAAGAAGCAGAACAAAAAGAGGCCGAATTTCAGCAGATGCTCGAACAG
                                                                 Section 39
                 (1825) 1825 1830      1840      1850      1860       1872
ClareAJ251507    (1665) CTTAAAAAGCAACAGGAAGAAGCTCAGGCAGTTGCGGCAGCATCAGCT
huNaIII18 (AK)   (1361) CTTAAAAAGCAACAGGAAGAAGCTCAGGCAGTTGCGGCAGCATCAGCT
JeongAF225987    (1825) CTTAAAAAGCAACAGGAAGAAGCTCAGGCAGTTGCGGCAGCATCAGCT
Consensus        (1825) CTTAAAAAGCAACAGGAAGAAGCTCAGGCAGTTGCGGCAGCATCAGCT
                                                                 Section 40
                 (1873) 1873   1880      1890      1900      1910      1920
ClareAJ251507    (1713) GCTTCAAGAGATTTCAGTGGAATAGGTGGGTTAGGAGAGCTGTTGGAA
huNaIII18 (AK)   (1409) GCTTCAAGAGATTTCAGTGGAATAGGTGGGTTAGGAGAGCTGTTGGAA
JeongAF225987    (1873) GCTTCAAGAGATTTCAGTGGAGTAGGTGGGTTAGGAGAGCTGTTGGAA
Consensus        (1873) GCTTCAAGAGATTTCAGTGGAATAGGTGGGTTAGGAGAGCTGTTGGAA
                                                                 Section 41
                 (1921) 1921      1930      1940      1950             1968
ClareAJ251507    (1761) AGTTCTTCAGAAGCATCAAAGTTGAGTTCCAAAAGTGCTAAAGAATGG
huNaIII18 (AK)   (1457) AGTTCTTCAGAAGCATCAAAGTTGAGTTCCAAAAGTGCTAAAGAATGG
JeongAF225987    (1921) AGTTCTTCAGAAGCATCAAAGTTGAGTTCCAAAGGTGCTAAAGAATGG
Consensus        (1921) AGTTCTTCAGAAGCATCAAAGTTGAGTTCCAAAAGTGCTAAAGAATGG
                                                                 Section 42
                 (1969) 1969       1980      1990      2000             2016
ClareAJ251507    (1809) AGGAACCGAAGGAAGAAAAGAAGACAGAGAGAGCACCTTGAAGGAAAC
huNaIII18 (AK)   (1505) AGGAACCGAAGGAAGAAAAGAAGACGGAGAGAGCACCTTGAAGGAAAC
JeongAF225987    (1969) AGGAACCGGAGGAAGAAAAGAAGACAGAGAGAGCACCTTGAAGGAAAC
Consensus        (1969) AGGAACCGAAGGAAGAAAAGAAGACAGAGAGAGCACCTTGAAGGAAAC
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Section 43

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(2017) 2017                2030        2040        2050        2064
ClareAJ251507 (1857) AACAAAGGAGAGAGAGACAGCTTTCCCAAATCCGAATCTGAAGACAGC
huNalII18 (AK) (1553) AACAAAGGAGAGAGAGACAGCTTTCCCAAATCCGAATCTGAAGACAGC
JeongAF225987    (2017) AACAAAGGAGAGAGAGACAGCTTTCCCAAATCCGAATCTGAAGACAGC
Consensus (2017) AACAAAGGAGAGAGAGACAGCTTTCCCAAATCCGAATCTGAAGACAGC
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Section 44

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(2065) 2065  2070        2080        2090        2100        2112
ClareAJ251507 (1905) GTCAAAAGAAGCAGCTTCCTTTTCTCCATGGATGGAAACAGACTGACC
huNalII18 (AK) (1601) GTCAAAAGAAGCAGCTTCCTTTTCTCCATGGATGGAAACAGACTGACC
JeongAF225987    (2065) GTCAAAAGAAGCAGCTTCCTTTTCTCCATGGATGGAAACAGACTGACC
Consensus (2065) GTCAAAAGAAGCAGCTTCCTTTTCTCCATGGATGGAAACAGACTGACC
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Section 45

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(2113) 2113      2120        2130        2140        2150        2160
ClareAJ251507 (1953) AGTGACAAAAAATTCTGCTCCCCTCATCAGTCTCTCTTGAGTATCCGT
huNalII18 (AK) (1649) AGTGACAAAAAATTCTGCTCCCCTCATCAGTCTCTCTTGAGTATCCGT
JeongAF225987    (2113) AGTGACAAAAAATTCTGCTCCCCTCATCAGTCTCTCTTGAGTATCCGT
Consensus (2113) AGTGACAAAAAATTCTGCTCCCCTCATCAGTCTCTCTTGAGTATCCGT
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Section 46

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(2161) 2161      2170        2180        2190        2208
ClareAJ251507 (2001) GGCTCCCTGTTTTCCCCAAGACGCAATAGCAAAACAAGCATTTTCAGT
huNalII18 (AK) (1697) GGCTCCCTGTTTTCCCCAAGACGCAATAGCAAAACAAGCATTTTCAGT
JeongAF225987    (2161) GGCTCCCTGTTTTCCCCAAGACGCAATAGCAAAACAAGCATTTTCAGT
Consensus (2161) GGCTCCCTGTTTTCCCCAAGACGCAATAGCAAAACAAGCATTTTCAGT
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Section 47

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(2209) 2209          2220        2230        2240        2256
ClareAJ251507 (2049) TTCAGAGGTCGGGCAAAGGATGTTGGATCTGAAAATGACTTTGCTGAT
huNalII18 (AK) (1745) TTCAGAGGTCGGGCAAAGGATGTTGGATCTGAAAATGACTTTGCTGAT
JeongAF225987    (2209) TTCAGAGGTCGGGCAAAGGATGTTGGATCTGAAAATGACTTTGCTGAT
Consensus (2209) TTCAGAGGTCGGGCAAAGGATGTTGGATCTGAAAATGACTTTGCTGAT
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Section 48

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(2257) 2257              2270        2280        2290        2304
ClareAJ251507 (2097) GATGAACACAGCACATTTGAAGAC[ ]GCGAAAGCAGGAGAGACTCACTG
huNalII18 (AK) (1793) GATGAACACAGCACATTTGAAGAC[ ]GCGAAAGCAGGAGAGACTCACTG
JeongAF225987    (2257) GATGAACACAGCACATTTGAAGACGGCGAAAGCAGGAGAGACTCACTG
Consensus (2257) GATGAACACAGCACATTTGAAGACAGCGAAAGCAGGAGAGACTCACTG
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Section 49

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(2305) 2305  2310        2320        2330        2340        2352
ClareAJ251507 (2145) TTTGTGCCGCACAGACATGGAGAGCGACGCAACAGTAACG---------
huNalII18 (AK) (1841) TTTGTGCCGCACAGACATGGAGAGCGACGCAACAGTAACGTTAGTCAG
JeongAF225987    (2305) TTTGTGCCGCACAGACATGGAGAGCGACGCAACAGTAACGTTAGTCAG
Consensus (2305) TTTGTGCCGCACAGACATGGAGAGCGACGCAACAGTAACGTTAGTCAG
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Section 50

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(2353) 2353       2360       2370       2380       2390       2400
ClareAJ251507 (2185) ----------------------------------------------------
huNalII18 (AK) (1889) GCCAGTATGTCATCCAGGATGGTGCCAGGGCTTCCAGCAAATGGGAAG
JeongAF225987  (2353) GCCAGTATGTCATCCAGGATGGTGCCAGGGCTTCCAGCAAATGGGAAG
Consensus (2353) GCCAGTATGTCATCCAGGATGGTGCCAGGGCTTCCAGCAAATGGGAAG
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Section 51

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(2401) 2401       2410       2420       2430       2448
ClareAJ251507 (2185) ----------------------------------------------------
huNalII18 (AK) (1937) ATGCACAGCACTGTGGATTGCAATGGTGTGGTTTCCTTGGTGGGTGGA
JeongAF225987  (2401) ATGCACAGCACTGTGGATTGCAATGGTGTGGTTTCCTTGGTGGGTGGA
Consensus (2401) ATGCACAGCACTGTGGATTGCAATGGTGTGGTTTCCTTGGTGGGTGGA
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Section 52

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(2449) 2449       2460       2470       2480       2496
ClareAJ251507 (2185) ----------------------------------------GCACC
huNalII18 (AK) (1985) CCTTCAGCTCTAACGTCACCTACTGGACAACTTCCCCCAGAGGCACC
JeongAF225987  (2449) CCTTCAGCTCTAACGTCACCTACTGGACAACTTCCCCCAGAGGCACC
Consensus (2449) CCTTCAGCTCTAACGTCACCTACTGGACAACTTCCCCCAGAGGGCACC
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Section 53

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(2497) 2497            2510       2520       2530       2544
ClareAJ251507 (2190) ACCAC[ ]GAAACGGAAGTCAGAAAGAGAAGGTTAAGCTCTTACCAGATT
huNalII18 (AK) (2033) ACCACAGAAACGGAAGTCAGAAAGAGAAGGTTAAGCTCTTACCAGATT
JeongAF225987  (2497) ACCAC[ ]GAAACGGAAGTCAGAAAGAGAAGGTTAAGCTCTTACCAGATT
Consensus (2497) ACCACTGAAACGGAAGTCAGAAAGAGAAGGTTAAGCTCTTACCAGATT
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Section 54

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(2545) 2545  2550       2560       2570       2580       2592
ClareAJ251507 (2238) TCAATGGAGATGCTGGAGGATTCCTCTGGAAGGCAAAGAGCCGTGAGC
huNalII18 (AK) (2081) TCAATGGAGATGCTGGAGGATTCCTCTGGAAGGCAAAGAGCCGTGAGC
JeongAF225987  (2545) TCAATGGAGATGCTGGAGGATTCCTCTGGAAGGCAAAGAGCCGTGAGC
Consensus (2545) TCAATGGAGATGCTGGAGGATTCCTCTGGAAGGCAAAGAGCCGTGAGC
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Section 55

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(2593) 2593       2600       2610       2620       2630       2640
ClareAJ251507 (2286) ATAGCCAGCATTCTGACCAACACAATGGAAGAACTTGAAGAATCTAGA
huNalII18 (AK) (2129) ATAGCCAGCATTCTGACCAACACAATGGAAGAACTTGAAGAATCTAGA
JeongAF225987  (2593) ATAGCCAGCATTCTGACCAACACAATGGAAGAACTTGAAGAATCTAGA
Consensus (2593) ATAGCCAGCATTCTGACCAACACAATGGAAGAACTTGAAGAATCTAGA
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Section 56

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(2641) 2641       2650       2660       2670       2688
ClareAJ251507 (2334) CAGAAATGTCCGCCATGCTGGTATAGATTTGCCAATGTGTTCTTGATC
huNalII18 (AK) (2177) CAGAAATGTCCGCCATGCTGGTATAGATTTGCCAATGTGTTCTTGATC
JeongAF225987  (2641) CAGAAATGTCCGCCATGCTGGTATAGATTTGCCAATGTGTTCTTGATC
Consensus (2641) CAGAAATGTCCGCCATGCTGGTATAGATTTGCCAATGTGTTCTTGATC
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Section 57

(2689)	2689	2700	2710	2720	2736	
ClareAJ251507 (2382)	TGGGACTGCTGTGATGCATGGTTAAAAGTAAAACATCTTGTGAATTTA					
huNalII18 (AK) (2225)	TGGGACTGCTGTGATGCATGGTTAAAAGTAAAACATCTTGTGAATTTA					
JeongAF225987 (2689)	TGGGACTGCTGTGATGCATGGTTAAAAGTAAAACATCTTGTGAATTTA					
Consensus (2689)	TGGGACTGCTGTGATGCATGGTTAAAAGTAAAACATCTTGTGAATTTA					

Section 58

(2737)	2737	2750	2760	2770	2784	
ClareAJ251507 (2430)	ATTGTTATGGATCCATTTGTTGATCTTGCCATCACTATTTGCATTGTC					
huNalII18 (AK) (2273)	ATTGTTATGGATCCATTTGTTGATCTTGCCATCACTATTTGCATTGTC					
JeongAF225987 (2737)	ATTGTTATGGATCCATTTGTTGATCTTGCCATCACTATTTGCATTGTC					
Consensus (2737)	ATTGTTATGGATCCATTTGTTGATCTTGCCATCACTATTTGCATTGTC					

Section 59

(2785)	2785	2790	2800	2810	2820	2832
ClareAJ251507 (2478)	TTAAATACCCTCTTTATGGCCATGGAGCACTACCCCATGACTGAGCAA					
huNalII18 (AK) (2321)	TTAAATACCCTCTTTATGGCCATGGAGCACTACCCCATGACTGAGCAA					
JeongAF225987 (2785)	TTAAATACCCTCTTTATGGCCATGGAGCACTACCCCATGACTGAGCAA					
Consensus (2785)	TTAAATACCCTCTTTATGGCCATGGAGCACTACCCCATGACTGAGCAA					

Section 60

(2833)	2833	2840	2850	2860	2870	2880
ClareAJ251507 (2526)	TTCAGTAGTGTGTTGACTGTAGGAAACCTGGTCTTTACTGGGATTTTC					
huNalII18 (AK) (2369)	TTCAGTAGTGTGTTGACTGTAGGAAACCTGGTCTTTACTGGGATTTTC					
JeongAF225987 (2833)	TTCAGTAGTGTGTTGACTGTAGGAAACCTGGTCTTTACTGGGATTTTC					
Consensus (2833)	TTCAGTAGTGTGTTGACTGTAGGAAACCTGGTCTTTACTGGGATTTTC					

Section 61

(2881)	2881	2890	2900	2910	2928	
ClareAJ251507 (2574)	ACAGCAGAAATGGTTCTCAAGATCATTGCCATGGATCCTTATTACTAT					
huNalII18 (AK) (2417)	ACAGCAGAAATGGTTCTCAAGATCATTGCCATGGATCCTTATTACTAT					
JeongAF225987 (2881)	ACAGCAGAAATGGTTCTCAAGATCATTGCCATGGATCCTTATTACTAT					
Consensus (2881)	ACAGCAGAAATGGTTCTCAAGATCATTGCCATGGATCCTTATTACTAT					

Section 62

(2929)	2929	2940	2950	2960	2976	
ClareAJ251507 (2622)	TTCCAAGAAGGCTGGAATATCTTTGATGGAATTATTGTCAGCCTCAGT					
huNalII18 (AK) (2465)	TTCCAAGAAGGCTGGAATATCTTTGATGGAATTATTGTCAGCCTCAGT					
JeongAF225987 (2929)	TTCCAAGAAGGCTGGAATATCTTTGATGGAATTATTGTCAGCCTCAGT					
Consensus (2929)	TTCCAAGAAGGCTGGAATATCTTTGATGGAATTATTGTCAGCCTCAGT					

Section 63

(2977)	2977	2990	3000	3010	3024	
ClareAJ251507 (2670)	TTAATGGAGCTTGGTCTGTCAAATGTGGAGGGATTGTCTGTACTGCGA					
huNalII18 (AK) (2513)	TTAATGGAGCTTGGTCTGTCAAATGTGGAGGGATTGTCTGTACTGCGA					
JeongAF225987 (2977)	TTAATGGAGCTTGGTCTGTCAAATGTGGAGGGATTGTCTGTACTGCGA					
Consensus (2977)	TTAATGGAGCTTGGTCTGTCAAATGTGGAGGGATTGTCTGTACTGCGA					

Section 64

	(3025)	3025	3030	3040	3050	3060 3072
ClareAJ251507	(2718)	TCATTCAGACTGCTTAGAGTTTTCAAGTTGGCAAAATCCTGGCCCACA				
huNalII18 (AK)	(2561)	TCATTCAGACTGCTTAGAGTTTTCAAGTTGGCAAAATCCTGGCCCACA				
JeongAF225987	(3025)	TCATTCAGACTGCTTAGAGTTTTCAAGTTGGCAAAATCCTGGCCCACA				
Consensus	(3025)	TCATTCAGACTGCTTAGAGTTTTCAAGTTGGCAAAATCCTGGCCCACA				

Section 65

	(3073)	3073	3080	3090	3100	3110 3120
ClareAJ251507	(2766)	CTAAATATGCTAATTAAGATCATTGGCAATTCTGTGGGGGCTCTAGGA				
huNalII18 (AK)	(2609)	CTAAATATGCTAATTAAGATCATTGGCAATTCTGTGGGGGCTCTAGGA				
JeongAF225987	(3073)	CTAAATATGCTAATTAAGATCATTGGCAATTCTGTGGGGGCTCTAGGA				
Consensus	(3073)	CTAAATATGCTAATTAAGATCATTGGCAATTCTGTGGGGGCTCTAGGA				

Section 66

	(3121)	3121	3130	3140	3150	3168
ClareAJ251507	(2814)	AACCTCACCTTGGTGTTGGCCATCATCGTCTTCATTTTTGCTGTGGTC				
huNalII18 (AK)	(2657)	AACCTCACCTTGGTGTTGGCCATCATCGTCTTCATTTTTGCTGTGGTC				
JeongAF225987	(3121)	AACCTCACCTTGGTGTTGGCCATCATCGTCTTCATTTTTGCTGTGGTC				
Consensus	(3121)	AACCTCACCTTGGTGTTGGCCATCATCGTCTTCATTTTTGCTGTGGTC				

Section 67

	(3169)	3169	3180	3190	3200	3216
ClareAJ251507	(2862)	GGCATGCAGCTCTTTGGTAAGAGCTACAAAGAATGTGTCTGCAAGATC				
huNalII18 (AK)	(2705)	GGCATGCAGCTCTTTGGTAAGAGCTACAAAGAATGTGTCTGCAAGATC				
JeongAF225987	(3169)	GGCATGCAGCTCTTTGGTAAGAGCTACAAAGAATGTGTCTGCAAGATC				
Consensus	(3169)	GGCATGCAGCTCTTTGGTAAGAGCTACAAAGAATGTGTCTGCAAGATC				

Section 68

	(3217)	3217	3230	3240	3250	3264
ClareAJ251507	(2910)	AATGATGACTGTACGCTCCCACGGTGGCACATGAACGACTTCTTCCAC				
huNalII18 (AK)	(2753)	AATGATGACTGTACGCTCCCACGGTGGCACATGAACGACTTCTTCCAC				
JeongAF225987	(3217)	AATGATGACTGTACGCTCCCACGGTGGCACATGAACGACTTCTTCCAC				
Consensus	(3217)	AATGATGACTGTACGCTCCCACGGTGGCACATGAACGACTTCTTCCAC				

Section 69

	(3265)	3265	3270	3280	3290	3300 3312
ClareAJ251507	(2958)	TCCTTCCTGATTGTGTTCCGCGTGCTGTGTGGAGAGTGGATAGAGACC				
huNalII18 (AK)	(2801)	TCCTTCCTGATTGTGTTCCGCGTGCTGTGTGGAGAGTGGATAGAGACC				
JeongAF225987	(3265)	TCCTTCCTGATTGTGTTCCGCGTGCTGTGTGGAGAGTGGATAGAGACC				
Consensus	(3265)	TCCTTCCTGATTGTGTTCCGCGTGCTGTGTGGAGAGTGGATAGAGACC				

Section 70

	(3313)	3313	3320	3330	3340	3350 3360
ClareAJ251507	(3006)	ATGTGGGACTGTATGGAGGTCGCTGGCCAAACCATGTGCCTTATTGTT				
huNalII18 (AK)	(2849)	ATGTGGGACTGTATGGAGGTCGCTGGCCAAACCATGTGCCTTATTGTT				
JeongAF225987	(3313)	ATGTGGGACTGTATGGAGGTCGCTGGCCAAACCATGTGCCTTATTGTT				
Consensus	(3313)	ATGTGGGACTGTATGGAGGTCGCTGGCCAAACCATGTGCCTTATTGTT				

Section 71

	(3361)	3361	3370	3380	3390	3408
ClareAJ251507	(3054)	TTCATGTTGGTCATGGTCATTGGAAACCTTGTGGTTCTGAACCTCTTT				
huNaIII18 (AK)	(2897)	TTCATGTTGGTCATGGTCATTGGAAACCTTGTGGTTCTGAACCTCTTT				
JeongAF225987	(3361)	TTCATGTTGGTCATGGTCATTGGAAACCTTGTGGTTCTGAACCTCTTT				
Consensus	(3361)	TTCATGTTGGTCATGGTCATTGGAAACCTTGTGGTTCTGAACCTCTTT				

Section 72

	(3409)	3409	3420	3430	3440	3456
ClareAJ251507	(3102)	CTGGCCTTATTGTTGAGTTCATTTAGCTCAGACAACCTTGCTGCTACT				
huNaIII18 (AK)	(2945)	CTGGCCTTATTGTTGAGTTCATTTAGCTCAGACAACCTTGCTGCTACT				
JeongAF225987	(3409)	CTGGCCTTATTATTGAGTTCATTTAGCTCAGACAACCTTGCTGCTACT				
Consensus	(3409)	CTGGCCTTATTGTTGAGTTCATTTAGCTCAGACAACCTTGCTGCTACT				

Section 73

	(3457)	3457	3470	3480	3490	3504
ClareAJ251507	(3150)	GATGATGACAATGAAATGAATAATCTGCAGATTGCAGTAGGAAGAATG				
huNaIII18 (AK)	(2993)	GATGATGACAATGAAATGAATAATCTGCAGATTGCAGTAGGAAGAATG				
JeongAF225987	(3457)	GATGATGACAATGAAATGAATAATCTGCAGATTGCAGTAGGAAGAATG				
Consensus	(3457)	GATGATGACAATGAAATGAATAATCTGCAGATTGCAGTAGGAAGAATG				

Section 74

	(3505)	3505 3510	3520	3530	3540	3552
ClareAJ251507	(3198)	CAAAAGGGAATTGATTATGTGAAAAATAAGATGCGGGAGTGTTTCCAA				
huNaIII18 (AK)	(3041)	CAAAAGGGAATTGATTATGTGAAAAATAAGATGCGGGAGTGTTTCCAA				
JeongAF225987	(3505)	CAAAAGGGAATTGATTATGTGAAAAATAAGATGCGGGAGTGTTTCCAA				
Consensus	(3505)	CAAAAGGGAATTGATTATGTGAAAAATAAGATGCGGGAGTGTTTCCAA				

Section 75

	(3553)	3553 3560	3570	3580	3590	3600
ClareAJ251507	(3246)	AAAGCCTTTTTTAGAAAGCCAAAAGTTATAGAAATCCATGAAGGCAAT				
huNaIII18 (AK)	(3089)	AAAGCCTTTTTTAGAAAGCCAAAAGTTATAGAAATCCATGAAGGCAAT				
JeongAF225987	(3553)	AAAGCCTTTTTTAGAAAGCCAAAAGTTATAGAAATCCATGAAGGCAAT				
Consensus	(3553)	AAAGCCTTTTTTAGAAAGCCAAAAGTTATAGAAATCCATGAAGGCAAT				

Section 76

	(3601)	3601	3610	3620	3630	3648
ClareAJ251507	(3294)	AAGATAGACAGCTGCATGTCCAATAATACTGGAATTGAAATAAGCAAA				
huNaIII18 (AK)	(3137)	AAGATAGACAGCTGCATGTCCAATAATACTGGAATTGAAATAAGCAAA				
JeongAF225987	(3601)	AAGATAGACAGCTGCATGTCCAATAATACTGGAATTGAAATAAGCAAA				
Consensus	(3601)	AAGATAGACAGCTGCATGTCCAATAATACTGGAATTGAAATAAGCAAA				

Section 77

	(3649)	3649	3660	3670	3680	3696
ClareAJ251507	(3342)	GAGCTTAATTATCTTAGAGATGGGAATGGAACCACCAGTGGTGTAGGT				
huNaIII18 (AK)	(3185)	GAGCTTAATTATCTTAGAGATGGGAATGGAACCACCAGTGGTGTAGGT				
JeongAF225987	(3649)	GAGCTTAATTATCTTAGAGATGGGAATGGAACCACCAGTGGTGTAGGT				
Consensus	(3649)	GAGCTTAATTATCTTAGAGATGGGAATGGAACCACCAGTGGTGTAGGT				

Section 78

	(3697)	3697 3710 3720 3730 3744
ClareAJ251507	(3390)	ACTGGAAGCAGTGTTGAAAAATACGTAATCGATGAAAATGATTATATG
huNalII18 (AK)	(3233)	ACTGGAAGCAGTGTTGAAAAATACGTAATCGATGAAAATGATTATATG
JeongAF225987	(3697)	ACTGGAAGCAGTGTTGAAAAATACGTAATCGATGAAAATGATTATATG
Consensus	(3697)	ACTGGAAGCAGTGTTGAAAAATACGTAATCGATGAAAATGATTATATG

Section 79

	(3745)	3745 3750 3760 3770 3780 3792
ClareAJ251507	(3438)	TCATTCATAAACAACCCCAGCCTCACCGTCACAGTGCCAATTGCTGTT
huNalII18 (AK)	(3281)	TCATTCATAAACAACCCCAGCCTCACCGTCACAGTGCCAATTGCTGTT
JeongAF225987	(3745)	TCATTCATAAACAACCCCAGCCTCACCGTCACAGTGCCAATTGCTGTT
Consensus	(3745)	TCATTCATAAACAACCCCAGCCTCACCGTCACAGTGCCAATTGCTGTT

Section 80

	(3793)	3793 3800 3810 3820 3830 3840
ClareAJ251507	(3486)	GGAGAGTCTGACTTTGAAAACTTAAATACTGAAGAGTTCAGCAGTGAG
huNalII18 (AK)	(3329)	GGAGAGTCTGACTTTGAAAACTTAAATACTGAAGAGTTCAGCAGTGAG
JeongAF225987	(3793)	GGAGAGTCTGACTTTGAAAACTTAAATACTGAAGAGTTCAGCAGTGAG
Consensus	(3793)	GGAGAGTCTGACTTTGAAAACTTAAATACTGAAGAGTTCAGCAGTGAG

Section 81

	(3841)	3841 3850 3860 3870 3888
ClareAJ251507	(3534)	TCAGAACTAGAAGAAAGCAAAGAGAAATTAAATGCAACCAGCTCATCT
huNalII18 (AK)	(3377)	TCAGAACTAGAAGAAAGCAAAGAGAAATTAAATGCAACCAGCTCATCT
JeongAF225987	(3841)	TCAGAACTAGAAGAAAGCAAAGAGAAATTAAATGCAACCAGCTCATCT
Consensus	(3841)	TCAGAACTAGAAGAAAGCAAAGAGAAATTAAATGCAACCAGCTCATCT

Section 82

	(3889)	3889 3900 3910 3920 3936
ClareAJ251507	(3582)	GAAGGAAGCACAGTTGATGTTGTTCTACCCCGAGAAGGTGAACAAGCT
huNalII18 (AK)	(3425)	GAAGGAAGCACAGTTGATGTTGTTCTACCCCGAGAAGGTGAACAAGCT
JeongAF225987	(3889)	GAAGGAAGCACAGTTGATGTTGTTCTACCCCGAGAAGGTGAACAAGCT
Consensus	(3889)	GAAGGAAGCACAGTTGATGTTGTTCTACCCCGAGAAGGTGAACAAGCT

Section 83

	(3937)	3937 3950 3960 3970 3984
ClareAJ251507	(3630)	GAAACTGAACCCGAAGAAGACCTTAAACCGGAAGCTTGTTTTACTGAA
huNalII18 (AK)	(3473)	GAAACTGAACCCGAAGAAGACCTTAAACCGGAAGCTTGTTTTACTGAA
JeongAF225987	(3937)	GAAACTGAACCCGAAGAAGACTTTAAACCGGAAGCTTGTTTTACTGAA
Consensus	(3937)	GAAACTGAACCCGAAGAAGACCTTAAACCGGAAGCTTGTTTTACTGAA

Section 84

	(3985)	3985 3990 4000 4010 4020 4032
ClareAJ251507	(3678)	GGATGTATTAAAAAGTTTCCATTCTGTCAAGTAAGTACAGAAGAAGGC
huNalII18 (AK)	(3521)	GGATGTATTAAAAAGTTTCCATTCTGTCAAGTAAGTACAGAAGAAGGC
JeongAF225987	(3985)	GGGTGTATTAAAAAGTTTCCATTCTGTCAAGTAAGTACAGAAGAAGGC
Consensus	(3985)	GGATGTATTAAAAAGTTTCCATTCTGTCAAGTAAGTACAGAAGAAGGC

Section 85

	(4033)	4033 4040 4050 4060 4070 4080
ClareAJ251507	(3726)	AAAGGGAAGATCTGGTGGAATCTTCGAAAAACCTGCTACAGTATTGTT
huNalII18 (AK)	(3569)	AAAGGGAAGATCTGGTGGAATCTTCGAAAAACCTGCTACAGTATTGTT
JeongAF225987	(4033)	AAAGGGAAGATCTGGTGGAATCTTCGAAAAACCTGCTACAGTATTGTT
Consensus	(4033)	AAAGGGAAGATCTGGTGGAATCTTCGAAAAACCTGCTACAGTATTGTT

Section 86

	(4081)	4081 4090 4100 4110 4128
ClareAJ251507	(3774)	GAGCACAACTGGTTTGAGACTTTCATTGTGTTCATGATCCTTCTCAGT
huNalII18 (AK)	(3617)	GAGCACAACTGGTTTGAGACTTTCATTGTGTTCATGATCCTTCTCAGT
JeongAF225987	(4081)	GAGCACAACTGGTTTGAGACTTTCATTGTGTTCATGATCCTTCTCAGT
Consensus	(4081)	GAGCACAACTGGTTTGAGACTTTCATTGTGTTCATGATCCTTCTCAGT

Section 87

	(4129)	4129 4140 4150 4160 4176
ClareAJ251507	(3822)	AGTGGTGCATTGGCCTTTGAAGATATATACATTGAACAGCGAAAGACT
huNalII18 (AK)	(3665)	AGTGGTGCATTGGCCTTTGAAGATATATACATTGAACAGCGAAAGACT
JeongAF225987	(4129)	AGTGGTGCATTGGCCTTTGAAGATATATACATTGAACAGCGAAAGACT
Consensus	(4129)	AGTGGTGCATTGGCCTTTGAAGATATATACATTGAACAGCGAAAGACT

Section 88

	(4177)	4177 4190 4200 4210 4224
ClareAJ251507	(3870)	ATCAAAACCATGCTAGAATATGCTGACAAAGTCTTTACCTATATATTC
huNalII18 (AK)	(3713)	ATCAAAACCATGCTAGAATATGCTGACAAAGTCTTTACCTATATATTC
JeongAF225987	(4177)	ATCAAAACCATGCTAGAATATGCTGACAAAGTCTTTACCTATATATTC
Consensus	(4177)	ATCAAAACCATGCTAGAATATGCTGACAAAGTCTTTACCTATATATTC

Section 89

	(4225)	4225 4230 4240 4250 4260 4272
ClareAJ251507	(3918)	ATTCTGGAAATGCTTCTCAAATGGGTTGCTTATGGATTTCAAACATAT
huNalII18 (AK)	(3761)	ATTCTGGAAATGCTTCTCAAATGGGTTGCTTATGGATTTCAAACATAT
JeongAF225987	(4225)	ATTCTGGAAATGCTTCTCAAATGGGTTGCTTATGGATTTCAAACATAT
Consensus	(4225)	ATTCTGGAAATGCTTCTCAAATGGGTTGCTTATGGATTTCAAACATAT

Section 90

	(4273)	4273 4280 4290 4300 4310 4320
ClareAJ251507	(3966)	TTCACTAATGCCTGGTGCTGGCTAGATTTCTTGATCGTTGATGTTTCT
huNalII18 (AK)	(3809)	TTCACTAATGCCTGGTGCTGGCTAGATTTCTTGATCGTTGATGTTTCT
JeongAF225987	(4273)	TTCACTAATGCCTGGTGCTGGCTAGATTTCTTGATCGTTGATGTTTCT
Consensus	(4273)	TTCACTAATGCCTGGTGCTGGCTAGATTTCTTGATCGTTGATGTTTCT

Section 91

	(4321)	4321 4330 4340 4350 4368
ClareAJ251507	(4014)	TTGGTTAGCCTGGTAGCCAATGCTCTTGGCTACTCAGAACTCGGTGCC
huNalII18 (AK)	(3857)	TTGGTTAGCCTGGTAGCCAATGCTCTTGGCTACTCAGAACTCGGTGCC
JeongAF225987	(4321)	TTGGTTAGCCTGGTAGCCAATGCTCTTGGCTACTCAGAACTCGGTGCC
Consensus	(4321)	TTGGTTAGCCTGGTAGCCAATGCTCTTGGCTACTCAGAACTCGGTGCC

Section 92

	(4369)	4369	4380	4390	4400	4416
ClareAJ251507	(4062)	ATCAAATCATTACGGACATTAAGAGCTTTAAGACCTCTAAGAGCCTTA				
huNalII18 (AK)	(3905)	ATCAAATCATTACGGACATTAAGAGCTTTAAGACCTCTAAGAGCCTTA				
JeongAF225987	(4369)	ATCAAATCATTACGGACATTAAGAGCTTTAAGACCTCTAAGAGCCTTA				
Consensus	(4369)	ATCAAATCATTACGGACATTAAGAGCTTTAAGACCTCTAAGAGCCTTA				

Section 93

	(4417)	4417	4430	4440	4450	4464
ClareAJ251507	(4110)	TCCCGGTTTGAAGGCATGAGGGTGGTTGTGAATGCTCTTGTTGGAGCA				
huNalII18 (AK)	(3953)	TCCCGGTTTGAAGGCATGAGGGTGGTTGTGAATGCTCTTGTTGGAGCA				
JeongAF225987	(4417)	TCCCGGTTTGAAGGCATGAGGGTGGTTGTGAATGCTCTTGTTGGAGCA				
Consensus	(4417)	TCCCGGTTTGAAGGCATGAGGGTGGTTGTGAATGCTCTTGTTGGAGCA				

Section 94

	(4465)	4465 4470	4480	4490	4500	4512
ClareAJ251507	(4158)	ATTCCCTCTATCATGAATGTGCTGTTGGTCTGTCTCATCTTCTGGTTG				
huNalII18 (AK)	(4001)	ATTCCCTCTATCATGAATGTGCTGTTGGTCTGTCTCATCTTCTGGTTG				
JeongAF225987	(4465)	ATTCCCTCTATCATGAATGTGCTGTTGGTCTGTCTCATCTTCTGGTTG				
Consensus	(4465)	ATTCCCTCTATCATGAATGTGCTGTTGGTCTGTCTCATCTTCTGGTTG				

Section 95

	(4513)	4513 4520	4530	4540	4550	4560
ClareAJ251507	(4206)	ATCTTTAGCATCATGGGTGTGAATTTGTTTGCTGGCAAGTTCTACCAC				
huNalII18 (AK)	(4049)	ATCTTTAGCATCATGGGTGTGAATTTGTTTGCTGGCAAGTTCTACCAC				
JeongAF225987	(4513)	ATCTTTAGCATCATGGGTGTGAATTTGTTTGCTGGCAAGTTCTACCAC				
Consensus	(4513)	ATCTTTAGCATCATGGGTGTGAATTTGTTTGCTGGCAAGTTCTACCAC				

Section 96

	(4561)	4561 4570	4580	4590		4608
ClareAJ251507	(4254)	TGTGTTAACATGACAACGGGTAACATGTTTGACATTAGTGATGTTAAC				
huNalII18 (AK)	(4097)	TGTGTTAACATGACAACGGGTAACATGTTTGACATTAGTGATGTTAAC				
JeongAF225987	(4561)	TGTGTTAACATGACAACGGGTAACATGTTTGACATTAGTGATGTTAAC				
Consensus	(4561)	TGTGTTAACATGACAACGGGTAACATGTTTGACATTAGTGATGTTAAC				

Section 97

	(4609)	4609	4620	4630	4640	4656
ClareAJ251507	(4302)	AATTTGAGTGACTGTCAGGCTCTTGGCAAGCAAGCTCGGTGGAAAAAC				
huNalII18 (AK)	(4145)	AATTTGAGTGACTGTCAGGCTCTTGGCAAGCAAGCTCGGTGGAAAAAC				
JeongAF225987	(4609)	AATTTGAGTGACTGTCAGGCTCTTGGCAAGCAAGCTCGGTGGAAAAAC				
Consensus	(4609)	AATTTGAGTGACTGTCAGGCTCTTGGCAAGCAAGCTCGGTGGAAAAAC				

Section 98

	(4657)	4657	4670	4680	4690	4704
ClareAJ251507	(4350)	GTGAAAGTAAACTTTGATAATGTTGGCGCTGGCTATCTTGCACTGCTT				
huNalII18 (AK)	(4193)	GTGAAAGTAAACTTTGATAATGTTGGCGCTGGCTATCTTGCACTGCTT				
JeongAF225987	(4657)	GTGAAAGTAAACTTTGATAATGTTGGCGCTGGCTATCTTGCACTGCTT				
Consensus	(4657)	GTGAAAGTAAACTTTGATAATGTTGGCGCTGGCTATCTTGCACTGCTT				

Section 99

	(4705)	4705 4710 4720 4730 4740 4752
ClareAJ251507	(4398)	CAAGTGGCCACATTTAAAGGCTGGATGGATATTATGTATGCAGCTGTT
huNalII18 (AK)	(4241)	CAAGTGGCCACATTTAAAGGCTGGATGGATATTATGTATGCAGCTGTT
JeongAF225987	(4705)	CAAGTGGCCACATTTAAAGGCTGGATGGATATTATGTATGCAGCTGTT
Consensus	(4705)	CAAGTGGCCACATTTAAAGGCTGGATGGATATTATGTATGCAGCTGTT

Section 100

	(4753)	4753 4760 4770 4780 4790 4800
ClareAJ251507	(4446)	GATTCACGAGATGTTAAACTTCAGCCTGTATATGAAGAAAATCTGTAC
huNalII18 (AK)	(4289)	GATTCACGAGATGTTAAACTTCAGCCTGTATATGAAGAAAATCTGTAC
JeongAF225987	(4753)	GATTCACGAGATGTTAAACTTCAGCCTGTATATGAAGAAAATCTGTAC
Consensus	(4753)	GATTCACGAGATGTTAAACTTCAGCCTGTATATGAAGAAAATCTGTAC

Section 101

	(4801)	4801 4810 4820 4830 4848
ClareAJ251507	(4494)	ATGTATTTATACTTTGTCATCTTTATCATCTTTGGGTCATTCTTCACT
huNalII18 (AK)	(4337)	ATGTATTTATACTTTGTCATCTTTATCATCTTTGGGTCATTCTTCACT
JeongAF225987	(4801)	ATGTATTTATACTTTGTCATCTTTATCATCTTTGGGTCATTCTTCACT
Consensus	(4801)	ATGTATTTATACTTTGTCATCTTTATCATCTTTGGGTCATTCTTCACT

Section 102

	(4849)	4849 4860 4870 4880 4896
ClareAJ251507	(4542)	CTGAATCTATTCATTGGTGTCATCATAGATAACTTCAACCAGCAGAAA
huNalII18 (AK)	(4385)	CTGAATCTATTCATTGGTGTCATCATAGATAACTTCAACCAGCAGAAA
JeongAF225987	(4849)	CTGAATCTATTCATTGGTGTCATCATAGATAACTTCAACCAGCAGAAA
Consensus	(4849)	CTGAATCTATTCATTGGTGTCATCATAGATAACTTCAACCAGCAGAAA

Section 103

	(4897)	4897 4910 4920 4930 4944
ClareAJ251507	(4590)	AAGAAGTTTGGAGGTCAAGACATCTTTATGACAGAGGAACAGAAAAAA
huNalII18 (AK)	(4433)	AAGAAGTTTGGAGGTCAAGACATCTTTATGACAGAGGAACAGAAAAAA
JeongAF225987	(4897)	AAGAAGTTTGGAGGTCAAGACATCTTTATGACAGAGGAACAGAAAAAA
Consensus	(4897)	AAGAAGTTTGGAGGTCAAGACATCTTTATGACAGAGGAACAGAAAAAA

Section 104

	(4945)	4945 4950 4960 4970 4980 4992
ClareAJ251507	(4638)	TATTACAATGCAATGAAGAAACTTGGATCCAAGAAACCTCAGAAACCC
huNalII18 (AK)	(4481)	TATTACAATGCAATGAAGAAACTTGGATCCAAGAAACCTCAGAAACCC
JeongAF225987	(4945)	TATTACAATGCAATGAAGAAACTTGGATCCAAGAAACCTCAGAAACCC
Consensus	(4945)	TATTACAATGCAATGAAGAAACTTGGATCCAAGAAACCTCAGAAACCC

Section 105

	(4993)	4993 5000 5010 5020 5030 5040
ClareAJ251507	(4686)	ATACCTCGCCCAGCAAACAAATTCCAAGGAATGGTCTTTGATTTTGTA
huNalII18 (AK)	(4529)	ATACCTCGCCCAGCAAACAAATTCCAAGGAATGGTCTTTGATTTTGTA
JeongAF225987	(4993)	ATACCTCGCCCAGCAAACAAATTCCAAGGAATGGTCTTTGATTTTGTA
Consensus	(4993)	ATACCTCGCCCAGCAAACAAATTCCAAGGAATGGTCTTTGATTTTGTA

Section 106

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                (5041) 5041       5050       5060       5070       5088
ClareAJ251507 (4734) ACCAGACAAGTCTTTGATATCAGCATCATGATCCTCATCTGCCTCAAC
huNalII18 (AK) (4577) ACCAGACAAGTCTTTGATATCAGCATCATGATCCTCATCTGCCTCAAC
JeongAF225987  (5041) ACCAGACAAGTCTTTGATATCAGCATCATGATCCTCATCTGCCTCAAC
Consensus (5041) ACCAGACAAGTCTTTGATATCAGCATCATGATCCTCATCTGCCTCAAC
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Section 107

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                (5089) 5089       5100       5110       5120       5136
ClareAJ251507 (4782) ATGGTCACCATGATGGTGGAAACGGATGACCAGGGCAAATACATGACC
huNalII18 (AK) (4625) ATGGTCACCATGATGGTGGAAACGGATGACCAGGGCAAATACATGACC
JeongAF225987  (5089) ATGGTCACCATGATGGTGGAAACGGATGACCAGGGCAAATACATGACC
Consensus (5089) ATGGTCACCATGATGGTGGAAACGGATGACCAGGGCAAATACATGACC
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Section 108

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                (5137) 5137       5150       5160       5170       5184
ClareAJ251507 (4830) CTAGTTTTGTCCCGGATCAACCTAGTGTTCATTGTTCTGTTCACTGGA
huNalII18 (AK) (4673) CTAGTTTTGTCCCGGATCAACCTAGTGTTCATTGTTCTGTTCACTGGA
JeongAF225987  (5137) CTAGTTTTGTCCCGGATCAACCTAGTGTTCATTGTTCTGTTCACTGGA
Consensus (5137) CTAGTTTTGTCCCGGATCAACCTAGTGTTCATTGTTCTGTTCACTGGA
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Section 109

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                (5185) 5185  5190       5200       5210       5220       5232
ClareAJ251507 (4878) GAATTTGTGCTGAAGCTCGTCTCCCTCAGACACTACTACTTCACTATA
huNalII18 (AK) (4721) GAATTTGTGCTGAGGCTCGTCTCCCTCAGACACTACTACTTCACTATA
JeongAF225987  (5185) GAATTTGTGCTGAAGCTCGTTTCCCTCAGACACTACTACTTCACTATA
Consensus (5185) GAATTTGTGCTGAAGCTCGTCTCCCTCAGACACTACTACTTCACTATA
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Section 110

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                (5233) 5233  5240       5250       5260       5270       5280
ClareAJ251507 (4926) GGCTGGAACATCTTTGACTTTGTGGTGGTGATTCTCTCCATTGTAGGT
huNalII18 (AK) (4769) GGCTGGAACATCTTTGACTTTGTGGTGGTGATTCTCTCCATTGTAGGT
JeongAF225987  (5233) GGCTGGAACATCTTTGACTTTGTGGTGGTGATTCTCTCCATTGTAGGT
Consensus (5233) GGCTGGAACATCTTTGACTTTGTGGTGGTGATTCTCTCCATTGTAGGT
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Section 111

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                (5281) 5281       5290       5300       5310       5328
ClareAJ251507 (4974) ATGTTTCTGGCTGAGATGATAGAAAAGTATTCTGTGTCCCCTACCTTG
huNalII18 (AK) (4817) ATGTTTCTGGCTGAGATGATAGAAAAGTATTCTGTGTCCCCTACCTTG
JeongAF225987  (5281) ATGTTTCTGGCTGAGATGATAGAAAAGTATTCTGTGTCCCCTACCTTG
Consensus (5281) ATGTTTCTGGCTGAGATGATAGAAAAGTATTTTGTGTCCCCTACCTTG
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Section 112

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                (5329) 5329       5340       5350       5360       5376
ClareAJ251507 (5022) TTCCGAGTGATCCGTCTTGCCAGGATTGGCCGAATCCTACGTCTGATC
huNalII18 (AK) (4865) TTCCGAGTGATCCGTCTTGCCAGGATTGGCCGAATCCTACGTCTGATC
JeongAF225987  (5329) TTCCGAGTGATCCGTCTTGCCAGGATTGGCCGAATCCTACGTCTGATC
Consensus (5329) TTCCGAGTGATCCGTCTTGCCAGGATTGGCCGAATCCTACGTCTGATC
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Section 113

	(5377)	5377	5390	5400	5410	5424
ClareAJ251507	(5070)	AAAGGAGCAAAGGGGATCCGCACGCTGCTCTTTGCTTTGATGATGTCC				
huNalII18 (AK)	(4913)	AAAGGAGCAAAGGGGATCCGCACGCTGCTCTTTGCTTTGATGATGTCC				
JeongAF225987	(5377)	AAAGGAGCAAAGGGGATCCGCACGCTGCTCTTTGCTTTGATGATGTCC				
Consensus	(5377)	AAAGGAGCAAAGGGGATCCGCACGCTGCTCTTTGCTTTGATGATGTCC				

Section 114

	(5425)	5425 5430	5440	5450	5460	5472
ClareAJ251507	(5118)	CTTCCTGCGTTGTTTAACATCGGCCTCCTGCTCTTCCTGGTCATGTTT				
huNalII18 (AK)	(4961)	CTTCCTGCGTTGTTTAACATCGGCCTCCTGCTCTTCCTGGTCATGTTT				
JeongAF225987	(5425)	CTTCCTGCGTTGTTTAACATCGGCCTCCTGCTCTTCCTGGTCATGTTT				
Consensus	(5425)	CTTCCTGCGTTGTTTAACATCGGCCTCCTGCTCTTCCTGGTCATGTTT				

Section 115

	(5473)	5473 5480	5490	5500	5510	5520
ClareAJ251507	(5166)	ATCTATGCCATCTTTGGGATGTCCAACTTTGCCTATGTTAAAAAGGAA				
huNalII18 (AK)	(5009)	ATCTATGCCATCTTTGGGATGTCCAACTTTGCCTATGTTAAAAAGGAA				
JeongAF225987	(5473)	ATCTATGCCATCTTTGGGATGTCCAACTTTGCCTATGTTAAAAAGGAA				
Consensus	(5473)	ATCTATGCCATCTTTGGGATGTCCAACTTTGCCTATGTTAAAAAGGAA				

Section 116

	(5521)	5521 5530	5540	5550		5568
ClareAJ251507	(5214)	GCTGGAATTGATGACATGTTCAACTTTGAGACCTTTGGCAACAGCATG				
huNalII18 (AK)	(5057)	GCTGGAATTGATGACATGTTCAACTTTGAGACCTTTGGCAACAGCATG				
JeongAF225987	(5521)	GCTGGAATTGATGACATGTTCAACTTTGAGACCTTTGGCAACAGCATG				
Consensus	(5521)	GCTGGAATTGATGACATGTTCAACTTTGAGACCTTTGGCAACAGCATG				

Section 117

	(5569)	5569 5580	5590	5600		5616
ClareAJ251507	(5262)	ATCTGCTTGTTCCAAATTACAACCTCTGCTGGCTGGGATGGATTGCTA				
huNalII18 (AK)	(5105)	ATCTGCTTGTTCCAAATTACAACCTCTGCTGGCTGGGATGGATTGCTA				
JeongAF225987	(5569)	ATCTGCTTGTTCCAAATTACAACCTCTGCTGGCTGGGATGGATTGCTA				
Consensus	(5569)	ATCTGCTTGTTCCAAATTACAACCTCTGCTGGCTGGGATGGATTGCTA				

Section 118

	(5617)	5617 5630	5640	5650		5664
ClareAJ251507	(5310)	GCACCTATTCTTAATAGTGCACCACCCGACTGTGACCCTGACACAATT				
huNalII18 (AK)	(5153)	GCACCTATTCTTAATAGTGCACCACCCGACTGTGACCCTGACACAATT				
JeongAF225987	(5617)	GCACCTATTCTTAATAGTGCACCACCCGACTGTGACCCTGACACAATT				
Consensus	(5617)	GCACCTATTCTTAATAGTGCACCACCCGACTGTGACCCTGACACAATT				

Section 119

	(5665)	5665 5670	5680	5690	5700	5712
ClareAJ251507	(5358)	CACCCTGGCAGCTCAGTTAAGGGAGAC[redacted]GTGGG[redacted]ACCCATCTGTTGGG				
huNalII18 (AK)	(5201)	CACCCTGGCAGCTCAGTTAAGGGAGAC[redacted]GTGGG[redacted]ACCCATCTGTTGGG				
JeongAF225987	(5665)	CACCCTGGCAGCTCAGTTAAGGGAGACCGTGGGGACCCATCTGTTGGG				
Consensus	(5665)	CACCCTGGCAGCTCAGTTAAGGGAGACTGTGGGAACCCATCTGTTGGG				

Section 120

	(5713)	5713 5720 5730 5740 5750 5760
ClareAJ251507	(5406)	ATTTTCTTTTTCGTCAGTTACATCATCATATCCTTCCTGGTTGTGGTG
huNalII18 (AK)	(5249)	ATTTTCTTTTTTGTCAGTTACATCATCATATCCTTCCTGGTTGTGGTG
JeongAF225987	(5713)	ATTTTCTTTTTTGTCAGTTACATCATCATATCCTTCCTGGTTGTGGTG
Consensus	(5713)	ATTTTCTTTTTTGTCAGTTACATCATCATATCCTTCCTGGTTGTGGTG

Section 121

	(5761)	5761 5770 5780 5790 5808
ClareAJ251507	(5454)	AACATGTACATCGCGGTCATCCTGGAGAACTTCAGTGTTGCTACTGAA
huNalII18 (AK)	(5297)	AACATGTACATCGCGGTCATCCTGGAGAACTTCAGTGTTGCTACTGAA
JeongAF225987	(5761)	AACATGTACATCGCGGTCATCCTGGAGAACTTCAGTGTTGCTACTGAA
Consensus	(5761)	AACATGTACATCGCGGTCATCCTGGAGAACTTCAGTGTTGCTACTGAA

Section 122

	(5809)	5809 5820 5830 5840 5856
ClareAJ251507	(5502)	GAAAGTGCAGAGCCCCTGAGTGAGGATGACTTTGAGATGTTCTATGAG
huNalII18 (AK)	(5345)	GAAAGTGCAGAGCCCCTGAGTGAGGATGACTTTGAGATGTTCTATGAG
JeongAF225987	(5809)	GAAAGTGCAGAGCCCCTGAGTGAGGATGACTTTGAGATGTTCTATGAG
Consensus	(5809)	GAAAGTGCAGAGCCCCTGAGTGAGGATGACTTTGAGATGTTCTATGAG

Section 123

	(5857)	5857 5870 5880 5890 5904
ClareAJ251507	(5550)	GTTTGGGAAAAGTTTGATCCCGATGCGACCCAGTTTATAGAGTTCTCT
huNalII18 (AK)	(5393)	GTTTGGGAAAAGTTTGATCCCGATGCGACCCAGTTTATAGAGTTCTCT
JeongAF225987	(5857)	GTTTGGGAAAAGTTTGATCCCGATGCGACCCAGTTTATAGAGTTCTCT
Consensus	(5857)	GTTTGGGAAAAGTTTGATCCCGATGCGACCCAGTTTATAGAGTTCTCT

Section 124

	(5905)	5905 5910 5920 5930 5940 5952
ClareAJ251507	(5598)	AAACTCTCTGATTTTGCAGCTGCCCTGGATCCTCCTCTTCTCATAGCA
huNalII18 (AK)	(5441)	AAACTCTCTGATTTTGCAGCTGCCCTGGATCCTCCTCTTCTCATAGCA
JeongAF225987	(5905)	AAACTCTCTGATTTTGCAGCTGCCCTGGATCCTCCTCTTCTCATAGCA
Consensus	(5905)	AAACTCTCTGATTTTGCAGCTGCCCTGGATCCTCCTCTTCTCATAGCA

Section 125

	(5953)	5953 5960 5970 5980 5990 6000
ClareAJ251507	(5646)	AAACCCAACAAAGTCCAGCTTATTGCCATGGATCTGCCCATGGTCAGT
huNalII18 (AK)	(5489)	AAACCCAACAAAGTCCAGCTTATTGCCATGGATCTGCCCATGGTCAGT
JeongAF225987	(5953)	AAACCCAACAAAGTCCAGCTTATTGCCATGGATCTGCCCATGGTCAGT
Consensus	(5953)	AAACCCAACAAAGTCCAGCTTATTGCCATGGATCTGCCCATGGTCAGT

Section 126

	(6001)	6001 6010 6020 6030 6048
ClareAJ251507	(5694)	GGTGACCGGATCCACTGTCTTGATATTTTATTTGCCTTTACAAAGCGT
huNalII18 (AK)	(5537)	GGTGACCGGATCCACTGTCTTGATATTTTATTTGCCTTTACAAAGCGT
JeongAF225987	(6001)	GGTGACCGGATCCACTGTCTTGATATTTTATTTGCCTTTACAAAGCGT
Consensus	(6001)	GGTGACCGGATCCACTGTCTTGATATTTTATTTGCCTTTACAAAGCGT

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Section 127
(6049)             6049     6060      6070      6080            6096
ClareAJ251507 (5742) GTTTTGGGTGAGAGTGGAGAGATGGATGCCCTTCGAATACAGATGGAA
huNaIII18 (AK) (5585) GTTTTGGGTGAGAGTGGAGAGATGGATGCCCTTCGAATACAGATGGAA
JeongAF225987 (6049) GTTTTGTGTGAGAGTGGAGAGATGGATGCCCTTCGAATACAGATGGAA
Consensus (6049)     GTTTTGGGTGAGAGTGGAGAGATGGATGCCCTTCGAATACAGATGGAA

Section 128
(6097)             6097         6110      6120      6130            6144
ClareAJ251507 (5790) GACAGGTTTATGGCATCAAACCCCTCCAAAGTCTCTTATGAGCCTATT
huNaIII18 (AK) (5633) GACAGGTTTATGGCATCAAACCCCTCCAAAGTCTCTTATGAGCCTATT
JeongAF225987 (6097) GACAGGTTTATGGCATCAAACCCCTCCAAAGTCTCTTATGAGCCTATT
Consensus (6097)     GACAGGTTTATGGCATCAAACCCCTCCAAAGTCTCTTATGAGCCTATT

Section 129
(6145)             6145 6150      6160      6170      6180          6192
ClareAJ251507 (5838) ACAACCACTTTGAAACGTAAACAAGAGGAGGTGTCTGCCGCTATCATT
huNaIII18 (AK) (5681) ACAACCACTTTGAAACGTAAACAAGAGGAGGTGTCTGCCGCTATCATT
JeongAF225987 (6145) ACAACCACTTTGAAACGTAAACAAGAGGAGGTGTCTGCCGCTATCATT
Consensus (6145)     ACAACCACTTTGAAACGTAAACAAGAGGAGGTGTCTGCCGCTATCATT

Section 130
(6193)             6193   6200      6210      6220      6230        6240
ClareAJ251507 (5886) CAGCGTAATTTCAGATGTTATCTTTTAAAGCAAAGGTTAAAAAATATA
huNaIII18 (AK) (5729) CAGCGTAATTTCAGATGTTATCTTTTAAAGCAAAGGTTAAAAAATATA
JeongAF225987 (6193) CAGCGTAATTTCAGATGTTATCTTTTAAAGCAAAGGTTAAAAAATATA
Consensus (6193)     CAGCGTAATTTCAGATGTTATCTTTTAAAGCAAAGGTTAAAAAATATA

Section 131
(6241)             6241     6250      6260      6270                6288
ClareAJ251507 (5934) TCAAGTAACTATAACAAAGAGGCAATTAAAGGGAGGATTGACTTACCT
huNaIII18 (AK) (5777) TCAAGTAACTATAACAAAGAGGCAATTAAAGGGAGGATTGACTTACCT
JeongAF225987 (6241) TCAAGTAACTATAACAAAGAGGCAATTAAAGGGAGGATTGACTTACCT
Consensus (6241)     TCAAGTAACTATAACAAAGAGGCAATTAAAGGGAGGATTGACTTACCT

Section 132
(6289)             6289         6300      6310      6320            6336
ClareAJ251507 (5982) ATAAAACAAGACATGATTATTGACAAACTAAATGGGAACTCCACTCCA
huNaIII18 (AK) (5825) ATAAAACAAGACATGATTATTGACAAACTAAATGGGAACTCCACTCCA
JeongAF225987 (6289) ATAAAACAAGACATGATTATTGACAAACTAAATGGGAACTCCACTCCA
Consensus (6289)     ATAAAACAAGACATGATTATTGACAAACTAAATGGGAACTCCACTCCA

Section 133
(6337)             6337         6350      6360      6370            6384
ClareAJ251507 (6030) GAAAAAACAGATGGGAGTTCCTCTACCACCTCTCCTCCTTCCTATGAT
huNaIII18 (AK) (5873) GAAAAAACAGATGGGAGTTCCTCTACCACCTCTCCTCCTTCCTATGAT
JeongAF225987 (6337) GAAAAAACAGATGGGAGTTCCTCTACCACCCCTCCTCCTTCCTATGAT
Consensus (6337)     GAAAAAACAGATGGGAGTTCCTCTACCACCTCTCCTCCTTCCTATGAT
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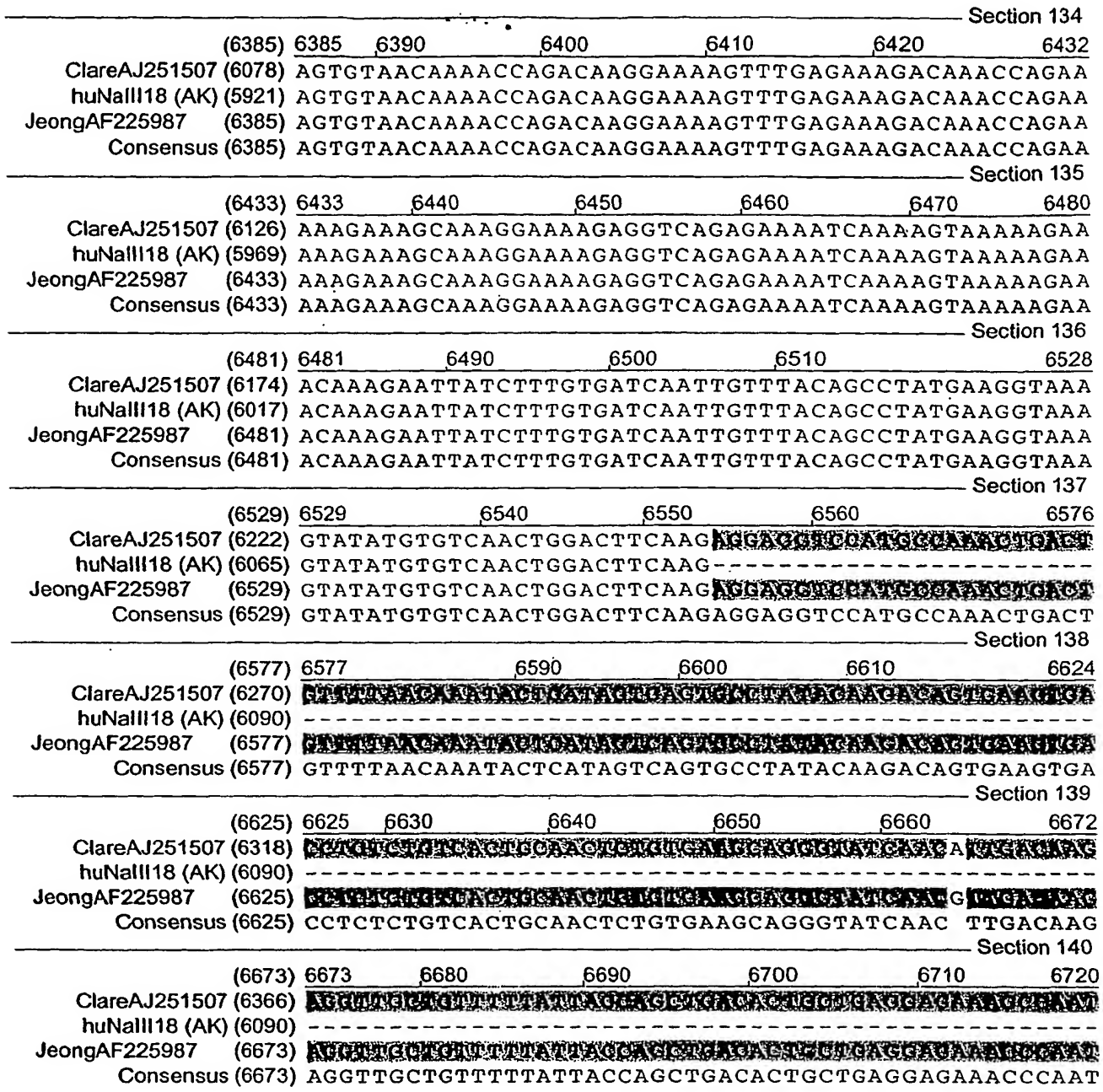
Section 134
(6385) 6385 6390 6400 6410 6420 6432
ClareAJ251507 (6078) AGTGTAACAAAACCAGACAAGGAAAAGTTTGAGAAAGACAAACCAGAA
huNalII18 (AK) (5921) AGTGTAACAAAACCAGACAAGGAAAAGTTTGAGAAAGACAAACCAGAA
JeongAF225987 (6385) AGTGTAACAAAACCAGACAAGGAAAAGTTTGAGAAAGACAAACCAGAA
Consensus (6385) AGTGTAACAAAACCAGACAAGGAAAAGTTTGAGAAAGACAAACCAGAA
Section 135
(6433) 6433 6440 6450 6460 6470 6480
ClareAJ251507 (6126) AAAGAAAGCAAAGGAAAAGAGGTCAGAGAAAATCAAAAGTAAAAAGAA
huNalII18 (AK) (5969) AAAGAAAGCAAAGGAAAAGAGGTCAGAGAAAATCAAAAGTAAAAAGAA
JeongAF225987 (6433) AAAGAAAGCAAAGGAAAAGAGGTCAGAGAAAATCAAAAGTAAAAAGAA
Consensus (6433) AAAGAAAGCAAAGGAAAAGAGGTCAGAGAAAATCAAAAGTAAAAAGAA
Section 136
(6481) 6481 6490 6500 6510 6528
ClareAJ251507 (6174) ACAAAGAATTATCTTTGTGATCAATTGTTTACAGCCTATGAAGGTAAA
huNalII18 (AK) (6017) ACAAAGAATTATCTTTGTGATCAATTGTTTACAGCCTATGAAGGTAAA
JeongAF225987 (6481) ACAAAGAATTATCTTTGTGATCAATTGTTTACAGCCTATGAAGGTAAA
Consensus (6481) ACAAAGAATTATCTTTGTGATCAATTGTTTACAGCCTATGAAGGTAAA
Section 137
(6529) 6529 6540 6550 6560 6576
ClareAJ251507 (6222) GTATATGTGTCAACTGGACTTCAAG
huNalII18 (AK) (6065) GTATATGTGTCAACTGGACTTCAAG----------
JeongAF225987 (6529) GTATATGTGTCAACTGGACTTCAAG
Consensus (6529) GTATATGTGTCAACTGGACTTCAAGAGGAGGTCCATGCCAAACTGACT
Section 138
(6577) 6577 6590 6600 6610 6624
ClareAJ251507 (6270)
huNalII18 (AK) (6090) ----------
JeongAF225987 (6577)
Consensus (6577) GTTTTAACAAATACTCATAGTCAGTGCCTATACAAGACAGTGAAGTGA
Section 139
(6625) 6625 6630 6640 6650 6660 6672
ClareAJ251507 (6318)
huNalII18 (AK) (6090) ----------
JeongAF225987 (6625)
Consensus (6625) CCTCTCTGTCACTGCAACTCTGTGAAGCAGGGTATCAAC TTGACAAG
Section 140
(6673) 6673 6680 6690 6700 6710 6720
ClareAJ251507 (6366)
huNalII18 (AK) (6090) ----------
JeongAF225987 (6673)
Consensus (6673) AGGTTGCTGTTTTTATTACCAGCTGACACTGCTGAGGAGAAACCCAAT

Section 141

(6721) 6721 6730 6740 6750 6768
ClareAJ251507 (6414) GGCTACCTAGACTATAGGGATAGTTGTGCAAAGTGAACATTGTAACTA
huNalII18 (AK) (6090) ----------
JeongAF225987 (6721) GGCTACCTAGACTATAGGGATAGTTGTGCAAAGTGAACATTGTAACTA
Consensus (6721) GGCTACCTAGACTATAGGGATAGTTGTGCAAAGTGAACATTGTAACTA

Section 142

(6769) 6769 6780 6790 6800 6816
ClareAJ251507 (6462) CACCAAACACCTTTAGTACAGTCCTTGCATCCATTCTATTTTTAACTT
huNalII18 (AK) (6090) ----------
JeongAF225987 (6769) CACCAAACACCTTTAGTACAGTCCTTGCATCCATTCTATTTTTAACTT
Consensus (6769) CACCAAACACCTTTAGTACAGTCCTTGCATCCATTCTATTTTTAACTT

Section 143

(6817) 6817 6830 6840 6850 6864
ClareAJ251507 (6510) CCATATCTGCCATATTTTTACAAAATTTGTTCTAGTGCATTTCCATGG
huNalII18 (AK) (6090) ----------
JeongAF225987 (6817) CCATATCTGCCATATTTTTACAAAATTTGTTCTAGTGCATTTCCATGG
Consensus (6817) CCATATCTGCCATATTTTTACAAAATTTGTTCTAGTGCATTTCCATGG

Section 144

(6865) 6865 6870 6880 6890 6900 6912
ClareAJ251507 (6558) TCCCCAATTCATAGTTTATTCATAATGCTATGTCACTATTTT------
huNalII18 (AK) (6090) ----------
JeongAF225987 (6865) TCCCCAATTCATAGTTTATTCATAATGCTATGTCACTATTTTTGTAAA
Consensus (6865) TCCCCAATTCATAGTTTATTCATAATGCTATGTCACTATTTT

Section 145

(6913) 6913 6920 6930 6940 6950 6960
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (6913) TGAGGTTTACGTTGAAGAAACAGTATACAAGAACCCTGTCTCTCAAAT
Consensus (6913)

Section 146

(6961) 6961 6970 6980 6990 7008
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (6961) GATCAGACAAAGGTGTTTTGCCAGAGAGATAAAATTTTTGCTCAAAAC
Consensus (6961)

Section 147

(7009) 7009 7020 7030 7040 7056
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (7009) CAGAAAAAGAATTGTAATGGCTACAGTTTCAGTTACTTCCATTTTCTA
Consensus (7009)

Section 148

(7057) 7057 7070 7080 7090 7104
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (7057) GATGGCTTTAATTTTGAAAGTATTTTAGTCTGTTATGTTTGTTTCTAT
Consensus (7057)

Section 149

(7105) 7105 7110 7120 7130 7140 7152
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (7105) CTGAACAGTTATGTGCCTGTAAAGTCTCCTCTAATATTTAAAGGATTA
Consensus (7105)

Section 150

(7153) 7153 7160 7170 7180 7190 7200
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (7153) TTTTTATGCAAAGTATTCTGTTTCAGCAAGTGCAAATTTTATTCTAAG
Consensus (7153)

Section 151

(7201) 7201 7210 7220 7230 7248
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (7201) TTTCAGAGCTCTATATTTAATTTAGGTCAAATGCTTTCCAAAAAGTAA
Consensus (7201)

Section 152

(7249) 7249 7260 7270 7280 7296
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (7249) TCTAATAAATCCATTCTAGAAAAATATATCTAAAGTATTGCTTTAGAA
Consensus (7249)

Section 153

(7297) 7297 7310 7320 7330 7344
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (7297) TAGTTGTTCCACTTTCTGCTGCAGTATTGCTTTGCCATCTTCTGCTCT
Consensus (7297)

Section 154

(7345) 7345 7350 7360 7370 7380 7392
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (7345) CAGCAAAGCTGATAGTCTATGTCAATTAAATACCCTATGTTATGTAAA
Consensus (7345)

Section 155

(7393) 7393 7400 7410 7420 7430 7440
ClareAJ251507 (6600) ----------
huNaIII18 (AK) (6090) ----------
JeongAF225987 (7393) TAGTTATTTTATCCTGTGGTGCATGTTTGGGCAAATATATATATAGCC
Consensus (7393)

Section 156

(7441) 7441 7450 7460 7470 7488
ClareAJ251507 (6600) ----------
huNaIII18 (AK) (6090) ----------
JeongAF225987 (7441) TGATAAACAACTTCTATTAAATCAAATATGTACCACAGTGTATGTGTC
Consensus (7441)

Section 157

(7489) 7489 7500 7510 7520 7536
ClareAJ251507 (6600) ----------
huNaIII18 (AK) (6090) ----------
JeongAF225987 (7489) TTTTGCAAGCTTCCAACAGGGATGTATCCTGTATCATTCATTAAACAT
Consensus (7489)

Section 158

(7537) 7537 7550 7560 7570 7584
ClareAJ251507 (6600) ----------
huNaIII18 (AK) (6090) ----------
JeongAF225987 (7537) AGTTTAAAGGCTATCACTAATGCATGTTAATATTGCCTATGCTGCTCT
Consensus (7537)

Section 159

(7585) 7585 7590 7600 7610 7620 7632
ClareAJ251507 (6600) ----------
huNaIII18 (AK) (6090) ----------
JeongAF225987 (7585) ATTTTACTCAATCCATTCTTCACAAGTCTTGGTTAAAGAATGTCACAT
Consensus (7585)

Section 160

(7633) 7633 7640 7650 7660 7670 7680
ClareAJ251507 (6600) ----------
huNaIII18 (AK) (6090) ----------
JeongAF225987 (7633) ATTGGTGATAGAATGAATTCAACCTGCTCTGTCCATTATGTCAAGCAG
Consensus (7633)

Section 161

(7681) 7681 7690 7700 7710 7728
ClareAJ251507 (6600) ----------
huNaIII18 (AK) (6090) ----------
JeongAF225987 (7681) AATAATTTGAAGCTATTTACAAACACCTTTACTTTTGCACTTTTAATT
Consensus (7681)

Section 162

(7729) 7729 7740 7750 7760 7776
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (7729) CAACATGAGTATCATATGGTATCTCTCTGGATTTCAAGGAAACACACT
Consensus (7729)

Section 163

(7777) 7777 7790 7800 7810 7824
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (7777) GGATACTGCCTACTGACAAAACCTATTCTTCATATTTTGCTAAAAATA
Consensus (7777)

Section 164

(7825) 7825 7830 7840 7850 7860 7872
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (7825) TGTCTAAAACTTGTTTAAATATAAATAATGTAAAAATATAATCAACTT
Consensus (7825)

Section 165

(7873) 7873 7880 7890 7900 7910 7920
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (7873) TATTTGTCAGCATTTTGTACATAAGAAAATTATTTTCAGGTTGATGAC
Consensus (7873)

Section 166

(7921) 7921 7930 7940 7950 7968
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (7921) ATCACAATTTATTTTACTTTATGCTTTTGCTTTTGATTTTTAATCACA
Consensus (7921)

Section 167

(7969) 7969 7980 7990 8000 8016
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (7969) ATTCCAAACTTTTGAATCCATAAGATTTTTCAATGGATAATTTCCTAA
Consensus (7969)

Section 168

(8017) 8017 8030 8040 8050 8064
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (8017) AATAAAAGTTAGATAATGGGTTTTATGGATTTCTTTGTTATAATATAT
Consensus (8017)

Section 169

(8065) 8065 8070 8080 8090 8100 8112
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (8065) TTTCTACCATTCCAATAGGAGATACATTGGTCAAACACTCAAACCTAG
Consensus (8065)

Section 170

(8113) 8113 8120 8130 8140 8150 8160
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (8113) ATCATTTTCTACCAACTATGGTTGCCTCAATATAACCTTTTATTCATA
Consensus (8113)

Section 171

(8161) 8161 8170 8180 8190 8208
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (8161) GATGTTTTTTTTTATTCAACTTTTGTAGTATTTACGTATGCAGACTAG
Consensus (8161)

Section 172

(8209) 8209 8220 8230 8240 8256
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (8209) TCTTATTTTTTTAATTCCTGCTGCACTAAAGCTATTACAAATATAACA
Consensus (8209)

Section 173

(8257) 8257 8270 8280 8290 8304
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (8257) TGGACTTTGTTCTTTTTAGCCATGAACAAAGTGGCAAAGTTGTGCAAT
Consensus (8257)

Section 174

(8305) 8305 8310 8320 8330 8340 8352
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (8305) TACCTAACATGATATAAATTTTTGTTTTTTGCACAAACCAAAAGTTTA
Consensus (8305)

Section 175

(8353) 8353 8360 8370 8380 8390 8400
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (8353) ATGTTAATTCTTTTTACAAAACTATTTACTGTAGTGTATTGAAGAACT
Consensus (8353)

Section 176

(8401) 8401 8410 8420 8430 8448
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (8401) GCATGCAGGGAATTGCTATTGCTAAAAAGAATGGTGAGCTACGTCATT
Consensus (8401)

Section 177

(8449) 8449 8460 8470 8480 8496
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (8449) ATTGAGCCAAAAGAATAAATTTCATTTTTTATTGCATTTCACTTATTG
Consensus (8449)

Section 178

(8497) 8497 8510 8520 8530 8544
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (8497) GGCTCTGGGGTTTTTTGTTTTTGTTTTTTGCTGTTGGCAGTTTAAAAT
Consensus (8497)

Section 179

(8545) 8545 8550 8560 8570 8580 8592
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (8545) ATATATAATTAATAAAACCTGTGCTTGATCTGACATTTGTATACATAA
Consensus (8545)

Section 180

(8593) 8593 8600 8610 8620 8630 8640
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (8593) AAGTTTACATGAATTTTACAACAAACTAGTGCATGATTCACCAAGCAG
Consensus (8593)

Section 181

(8641) 8641 8650 8660 8670 8688
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (8641) TACTACAGAACAAAGGCAAATTAAAAGCAGCTTTGTGAACTTTTATGT
Consensus (8641)

Section 182

(8689) 8689 8700 8710 8720 8736
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (8689) GTGCAAAGGATCAAGTTCACATGTTCCAACTTTCAGGTTTGATAATAA
Consensus (8689)

Section 183

(8737) 8737 8750 8760 8770 8784
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (8737) TAGTAGTAACCACCTACAATAGCTTTCAATTTCAATTAACTCCCTTGG
Consensus (8737)

Section 184

(8785) 8785 8790 8800 8810 8820 8832
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (8785) CTATAAGCATCTAAACTCATCTTCTTTCAATATAATTGATGCTATCTC
Consensus (8785)

Section 185

(8833) 8833 8840 8850 8860 8870 8880
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (8833) CTAATTACTTGGTGGCTAATAAATGTTACATTCTTTGTTACTTAAATG
Consensus (8833)

Section 186

(8881) 8881 8890 8900 8910 8928
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (8881) CATTATATAAACTCCTATGTATACATAAGGTATTAATGATATAGTTAT
Consensus (8881)

Section 187

(8929) 8929 8940 8950 8960 8976
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (8929) TGAGAATTTATATTAACTTTTTTTTCAAGAACCCTTGGATTTATGTGA
Consensus (8929)

Section 188

(8977) 8977 8990 9000 9010 9024
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (8977) GGTCAAAACCAAACTCTTATTCTCAGTGGAAAACTCCAGTTGTAATGC
Consensus (8977)

Section 189

(9025) 9025 9030 9040 9050 9060 9072
ClareAJ251507 (6600) ----------
huNalII18 (AK) (6090) ----------
JeongAF225987 (9025) ATATTTTTAAAGACAATTTGGATCTAAATATGTATTTCATAATTCTCC
Consensus (9025)

Section 190

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                (9073) 9073       9080       9090       9100       9110       9120
ClareAJ251507   (6600) ----------------------------------------------------------
huNalII18 (AK)  (6090) ----------------------------------------------------------
JeongAF225987   (9073) CATAATAAATTATATAAGGTGGAAAAAAAAAAAAAAAAAAAAAAAAA
Consensus       (9073)
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Section 191

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                (9121) 9123
ClareAJ251507   (6600) ---
huNalII18 (AK)  (6090) ---
JeongAF225987   (9121) AAA
Consensus       (9121)
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Section 1

	(1) 1 10 20 30 40
ClareAJ251507protein	(1) MAQALLVPPGPESFRLFTRESLAAIEKRAAEEKAKKPKKE
Translation of huNalII18 (AK)	(1) MAQALLVPPGPESFRLFTRESLAAIEKRAAEEKAKKPKKE
Translation of JeongAF225987	(1) MAQALLVPPGPESFRLFTRESLAAIEKRAAEEKAKKPKKE
Consensus	(1) MAQALLVPPGPESFRLFTRESLAAIEKRAAEEKAKKPKKE

Section 2

	(41) 41 50 60 70 80
ClareAJ251507protein	(41) QDNDDENKPKPNSDLEAGKNLPFIYGDIPPEMVSEPLEDL
Translation of huNalII18 (AK)	(41) QDNDDENKPKPNSDLEAGKNLPFIYGDIPPEMVSEPLEDL
Translation of JeongAF225987	(41) QDNDDENKPKPNSDLEAGKNLPFIYGDIPPEMVSEPLEDL
Consensus	(41) QDNDDENKPKPNSDLEAGKNLPFIYGDIPPEMVSEPLEDL

Section 3

	(81) 81 90 100 110 120
ClareAJ251507protein	(81) DPYYINKKTFIVMNKGKAIFRFSATSALYILTPLNPVRKI
Translation of huNalII18 (AK)	(81) DPYYINKKTFIVMNKGKAIFRFSATSALYILTPLNPVRKI
Translation of JeongAF225987	(81) DPYYINKKTFIVMNKGKAIFRFSATSALYILTPLNPVRKI
Consensus	(81) DPYYINKKTFIVMNKGKAIFRFSATSALYILTPLNPVRKI

Section 4

	(121) 121 130 140 150 160
ClareAJ251507protein	(121) AIKILVHSLFSMLIMCTILTNCVFMTLSNPPDWTKNVEYT
Translation of huNalII18 (AK)	(121) AIKILVHSLFSMLIMCTILTNCVFMTLSNPPDWTKNVEYT
Translation of JeongAF225987	(121) AIKILVHSLFSMLIMCTILTNCVFMTLSNPPDWTKNVEYT
Consensus	(121) AIKILVHSLFSMLIMCTILTNCVFMTLSNPPDWTKNVEYT

Section 5

	(161) 161 170 180 190 200
ClareAJ251507protein	(161) FTGIYTFESLIKILARGFCLEDFTFLRDPWNWLDFSVIVM
Translation of huNalII18 (AK)	(161) FTGIYTFESLIKILARGFCLEDFTFLRDPWNWLDFSVIVM
Translation of JeongAF225987	(161) FTGIYTFESLIKILARGFCLEDFTFLRDPWNWLDFSVIVM
Consensus	(161) FTGIYTFESLIKILARGFCLEDFTFLRDPWNWLDFSVIVM

Section 6

	(201) 201 210 220 230 240
ClareAJ251507protein	(201) AYVTEFVSLGNVSALRTFRVLRALKTISVIPGLKTIVGAL
Translation of huNalII18 (AK)	(201) AYVTEFVSLGNVSALRTFRVLRALKTISVIPGLKTIVGAL
Translation of JeongAF225987	(201) AYVTEFVDLGNVSALRTFRVLRALKTISVIPGLKTIVGAL
Consensus	(201) AYVTEFVSLGNVSALRTFRVLRALKTISVIPGLKTIVGAL

Section 7

	(241) 241 250 260 270 280
ClareAJ251507protein	(241) IQSVKKLSDVMILTVFCLSVFALIGLQLFMGNLRNKCLQW
Translation of huNalII18 (AK)	(241) IQSVKKLSDVMILTVFCLSVFALIGLQLFMGNLRNKCLQW
Translation of JeongAF225987	(241) IQSVKKLSDVMILTVFCLSVFALIGLQLFMGNLRNKCLQW
Consensus	(241) IQSVKKLSDVMILTVFCLSVFALIGLQLFMGNLRNKCLQW

Section 8

	(281)	281 290 300 310 320
ClareAJ251507protein	(281)	PPSDSAFETNTTSYFNGTMDSNGTFVNVTMSTFNWKDYIG
Translation of huNalII18 (AK)	(281)	PPSDSAFETNTTSYFNGTMDSNGTFVNVTMSTFNWKDYIG
Translation of JeongAF225987	(281)	PPSDSAFETNTTSYFNGTMDSNGTFVNVTMSTFNWKDYIG
Consensus	(281)	PPSDSAFETNTTSYFNGTMDSNGTFVNVTMSTFNWKDYIG

Section 9

	(321)	321 330 340 350 360
ClareAJ251507protein	(321)	DDSHFYVLDGQKDPLLCGNGSDAGQCPEGYICVKAGRNPN
Translation of huNalII18 (AK)	(321)	DDSHFYVLDGQKDPLLCGNGSDAGQCPEGYICVKAGRNPN
Translation of JeongAF225987	(321)	DDSHFYVLDGQKDPLLCGNGSDAGQCPEGYICVKAGRNPN
Consensus	(321)	DDSHFYVLDGQKDPLLCGNGSDAGQCPEGYICVKAGRNPN

Section 10

	(361)	361 370 380 390 400
ClareAJ251507protein	(361)	YGYTSFDTFSWAFLSLFRLMTQDYWENLYQLTLRAAGKTY
Translation of huNalII18 (AK)	(361)	YGYTSFDTFSWAFLSLFRLMTQDYWENLYQLTLRAAGKTY
Translation of JeongAF225987	(361)	YGYTSFDTFSWAFLSLFRLMTQDYWENLYQLTLRAAGKTY
Consensus	(361)	YGYTSFDTFSWAFLSLFRLMTQDYWENLYQLTLRAAGKTY

Section 11

	(401)	401 410 420 430 440
ClareAJ251507protein	(401)	MIFFVLVIFLGSFYLVNLILAVVAMAYEEQNQATLEEAEQ
Translation of huNalII18 (AK)	(401)	MIFFVLVIFLGSFYLVNLILAVVAMAYEEQNQATLEEAEQ
Translation of JeongAF225987	(401)	MIFFVLVIFLGSFYLVNLILAVVAMAYEEQNQATLEEAEQ
Consensus	(401)	MIFFVLVIFLGSFYLVNLILAVVAMAYEEQNQATLEEAEQ

Section 12

	(441)	441 450 460 470 480
ClareAJ251507protein	(441)	KEAEFQQMLEQLKKQQEEAQAVAAASAASRDFSGIGGLGE
Translation of huNalII18 (AK)	(441)	KEAEFQQMLEQLKKQQEEAQAVAAASAASRDFSGIGGLGE
Translation of JeongAF225987	(441)	KEAEFQQMLEQLKKQQEEAQAVAAASAASRDFSG[redacted]GGLGE
Consensus	(441)	KEAEFQQMLEQLKKQQEEAQAVAAASAASRDFSGIGGLGE

Section 13

	(481)	481 490 500 510 520
ClareAJ251507protein	(481)	LLESSSEASKLSSKSAKEWRNRRKKRRQREHLEGNNKGER
Translation of huNalII18 (AK)	(481)	LLESSSEASKLSSKSAKEWRNRRKKRRRREHLEGNNKGER
Translation of JeongAF225987	(481)	LLESSSEASKLSSKGAKEWRNRRKKRRQREHLEGNNKGER
Consensus	(481)	LLESSSEASKLSSKSAKEWRNRRKKRRQREHLEGNNKGER

Section 14

	(521)	521 530 540 550 560
ClareAJ251507protein	(521)	DSFPKSESEDSVKRSSFLFSMDGNRLTSDKKFCSPHQSLL
Translation of huNalII18 (AK)	(521)	DSFPKSESEDSVKRSSFLFSMDGNRLTSDKKFCSPHQSLL
Translation of JeongAF225987	(521)	DSFPKSESEDSVKRSSFLFSMDGNRLTSDKKFCSPHQSLL
Consensus	(521)	DSFPKSESEDSVKRSSFLFSMDGNRLTSDKKFCSPHQSLL

Section 15

	(561)	561 570 580 590 600
ClareAJ251507protein	(561)	SIRGSLFSPRRNSKTSIFSFRGRAKDVGSENDFADDEHST
Translation of huNalII18 (AK)	(561)	SIRGSLFSPRRNSKTSIFSFRGRAKDVGSENDFADDEHST
Translation of JeongAF225987	(561)	SIRGSLFSPRRNSKTSIFSFRGRAKDVGSENDFADDEHST
Consensus	(561)	SIRGSLFSPRRNSKTSIFSFRGRAKDVGSENDFADDEHST

Section 16

	(601)	601 610 620 630 640
ClareAJ251507protein	(601)	FEDSESRRDSLFVPHRHGERRNS----------
Translation of huNalII18 (AK)	(601)	FEDSESRRDSLFVPHRHGERRNS**NVSQASMSSRMVPGLPA**
Translation of JeongAF225987	(601)	FEDGESRRDSLFVPHRHGERRNS**NVSQASMSSRMVPGLPA**
Consensus	(601)	FEDSESRRDSLFVPHRHGERRNSNVSQASMSSRMVPGLPA

Section 17

	(641)	641 650 660 670 680
ClareAJ251507protein	(624)	----------NGTTTETE
Translation of huNalII18 (AK)	(641)	**NGKMHSTVDCNGVVSLVGGPSALTSPTGQLPPE**GTTTETE
Translation of JeongAF225987	(641)	**NGKMHSTVDCNGVVSLVGGPSALTSPTGQLPPE**GTTTETE
Consensus	(641)	NGKMHSTVDCNGVVSLVGGPSALTSPTGQLPPEGTTTETE

Section 18

	(681)	681 690 700 710 720
ClareAJ251507protein	(632)	VRKRRLSSYQISMEMLEDSSGRQRAVSIASILTNTMEELE
Translation of huNalII18 (AK)	(681)	VRKRRLSSYQISMEMLEDSSGRQRAVSIASILTNTMEELE
Translation of JeongAF225987	(681)	VRKRRLSSYQISMEMLEDSSGRQRAVSIASILTNTMEELE
Consensus	(681)	VRKRRLSSYQISMEMLEDSSGRQRAVSIASILTNTMEELE

Section 19

	(721)	721 730 740 750 760
ClareAJ251507protein	(672)	ESRQKCPPCWYRFANVFLIWDCCDAWLKVKHLVNLIVMDP
Translation of huNalII18 (AK)	(721)	ESRQKCPPCWYRFANVFLIWDCCDAWLKVKHLVNLIVMDP
Translation of JeongAF225987	(721)	ESRQKCPPCWYRFANVFLIWDCCDAWLKVKHLVNLIVMDP
Consensus	(721)	ESRQKCPPCWYRFANVFLIWDCCDAWLKVKHLVNLIVMDP

Section 20

	(761)	761 770 780 790 800
ClareAJ251507protein	(712)	FVDLAITICIVLNTLFMAMEHYPMTEQFSSVLTVGNLVFT
Translation of huNalII18 (AK)	(761)	FVDLAITICIVLNTLFMAMEHYPMTEQFSSVLTVGNLVFT
Translation of JeongAF225987	(761)	FVDLAITICIVLNTLFMAMEHYPMTEQFSSVLTVGNLVFT
Consensus	(761)	FVDLAITICIVLNTLFMAMEHYPMTEQFSSVLTVGNLVFT

Section 21

	(801)	801 810 820 830 840
ClareAJ251507protein	(752)	GIFTAEMVLKIIAMDPYYYFQEGWNIFDGIIVSLSLMELG
Translation of huNalII18 (AK)	(801)	GIFTAEMVLKIIAMDPYYYFQEGWNIFDGIIVSLSLMELG
Translation of JeongAF225987	(801)	GIFTAEMVLKIIAMDPYYYFQEGWNIFDGIIVSLSLMELG
Consensus	(801)	GIFTAEMVLKIIAMDPYYYFQEGWNIFDGIIVSLSLMELG

Section 22

	(841)	841 850 860 870 880
ClareAJ251507protein	(792)	LSNVEGLSVLRSFRLLRVFKLAKSWPTLNMLIKIIGNSVG
Translation of huNalII18 (AK)	(841)	LSNVEGLSVLRSFRLLRVFKLAKSWPTLNMLIKIIGNSVG
Translation of JeongAF225987	(841)	LSNVEGLSVLRSFRLLRVFKLAKSWPTLNMLIKIIGNSVG
Consensus	(841)	LSNVEGLSVLRSFRLLRVFKLAKSWPTLNMLIKIIGNSVG

Section 23

	(881)	881 890 900 910 920
ClareAJ251507protein	(832)	ALGNLTLVLAIIVFIFAVVGMQLFGKSYKECVCKINDDCT
Translation of huNalII18 (AK)	(881)	ALGNLTLVLAIIVFIFAVVGMQLFGKSYKECVCKINDDCT
Translation of JeongAF225987	(881)	ALGNLTLVLAIIVFIFAVVGMQLFGKSYKECVCKINDDCT
Consensus	(881)	ALGNLTLVLAIIVFIFAVVGMQLFGKSYKECVCKINDDCT

Section 24

	(921)	921 930 940 950 960
ClareAJ251507protein	(872)	LPRWHMNDFFHSFLIVFRVLCGEWIETMWDCMEVAGQTMC
Translation of huNalII18 (AK)	(921)	LPRWHMNDFFHSFLIVFRVLCGEWIETMWDCMEVAGQTMC
Translation of JeongAF225987	(921)	LPRWHMNDFFHSFLIVFRVLCGEWIETMWDCMEVAGQTMC
Consensus	(921)	LPRWHMNDFFHSFLIVFRVLCGEWIETMWDCMEVAGQTMC

Section 25

	(961)	961 970 980 990 1000
ClareAJ251507protein	(912)	LIVFMLVMVIGNLVVLNLFLALLLSSFSSDNLAATDDDNE
Translation of huNalII18 (AK)	(961)	LIVFMLVMVIGNLVVLNLFLALLLSSFSSDNLAATDDDNE
Translation of JeongAF225987	(961)	LIVFMLVMVIGNLVVLNLFLALLLSSFSSDNLAATDDDNE
Consensus	(961)	LIVFMLVMVIGNLVVLNLFLALLLSSFSSDNLAATDDDNE

Section 26

	(1001)	1001 1010 1020 1030 1040
ClareAJ251507protein	(952)	MNNLQIAVGRMQKGIDYVKNKMRECFQKAFFRKPKVIEIH
Translation of huNalII18 (AK)	(1001)	MNNLQIAVGRMQKGIDYVKNKMRECFQKAFFRKPKVIEIH
Translation of JeongAF225987	(1001)	MNNLQIAVGRMQKGIDYVKNKMRECFQKAFFRKPKVIEIH
Consensus	(1001)	MNNLQIAVGRMQKGIDYVKNKMRECFQKAFFRKPKVIEIH

Section 27

	(1041)	1041 1050 1060 1070 1080
ClareAJ251507protein	(992)	EGNKIDSCMSNNTGIEISKELNYLRDGNGTTSGVGTGSSV
Translation of huNalII18 (AK)	(1041)	EGNKIDSCMSNNTGIEISKELNYLRDGNGTTSGVGTGSSV
Translation of JeongAF225987	(1041)	EGNKIDSCMSNNTGIEISKELNYLRDGNGTTSGVGTGSSV
Consensus	(1041)	EGNKIDSCMSNNTGIEISKELNYLRDGNGTTSGVGTGSSV

Section 28

	(1081)	1081 1090 1100 1110 1120
ClareAJ251507protein	(1032)	EKYVIDENDYMSFINNPSLTVTVPIAVGESDFENLNTEEF
Translation of huNalII18 (AK)	(1081)	EKYVIDENDYMSFINNPSLTVTVPIAVGESDFENLNTEEF
Translation of JeongAF225987	(1081)	EKYVIDENDYMSFINNPSLTVTVPIAVGESDFENLNTEEF
Consensus	(1081)	EKYVIDENDYMSFINNPSLTVTVPIAVGESDFENLNTEEF

Section 29

	(1121)	1121	1130	1140	1150	1160
ClareAJ251507protein	(1072)	SSESELEESKEKLNATSSSEGSTVDVVLPREGEQAETEPE				
Translation of huNaIII18 (AK)	(1121)	SSESELEESKEKLNATSSSEGSTVDVVLPREGEQAETEPE				
Translation of JeongAF225987	(1121)	SSESELEESKEKLNATSSSEGSTVDVVLPREGEQAETEPE				
Consensus	(1121)	SSESELEESKEKLNATSSSEGSTVDVVLPREGEQAETEPE				

Section 30

	(1161)	1161	1170	1180	1190	1200
ClareAJ251507protein	(1112)	EDLKPEACFTEGCIKKFPFCQVSTEEGKGKIWWNLRKTCY				
Translation of huNaIII18 (AK)	(1161)	EDLKPEACFTEGCIKKFPFCQVSTEEGKGKIWWNLRKTCY				
Translation of JeongAF225987	(1161)	EDFKPEACFTEGCIKKFPFCQVSTEEGKGKIWWNLRKTCY				
Consensus	(1161)	EDLKPEACFTEGCIKKFPFCQVSTEEGKGKIWWNLRKTCY				

Section 31

	(1201)	1201	1210	1220	1230	1240
ClareAJ251507protein	(1152)	SIVEHNWFETFIVFMILLSSGALAFEDIYIEQRKTIKTML				
Translation of huNaIII18 (AK)	(1201)	SIVEHNWFETFIVFMILLSSGALAFEDIYIEQRKTIKTML				
Translation of JeongAF225987	(1201)	SIVEHNWFETFIVFMILLSSGALAFEDIYIEQRKTIKTML				
Consensus	(1201)	SIVEHNWFETFIVFMILLSSGALAFEDIYIEQRKTIKTML				

Section 32

	(1241)	1241	1250	1260	1270	1280
ClareAJ251507protein	(1192)	EYADKVFTYIFILEMLLKWVAYGFQTYFTNAWCWLDFLIV				
Translation of huNaIII18 (AK)	(1241)	EYADKVFTYIFILEMLLKWVAYGFQTYFTNAWCWLDFLIV				
Translation of JeongAF225987	(1241)	EYADKVFTYIFILEMLLKWVAYGFQTYFTNAWCWLDFLIV				
Consensus	(1241)	EYADKVFTYIFILEMLLKWVAYGFQTYFTNAWCWLDFLIV				

Section 33

	(1281)	1281	1290	1300	1310	1320
ClareAJ251507protein	(1232)	DVSLVSLVANALGYSELGAIKSLRTLRALRPLRALSRFEG				
Translation of huNaIII18 (AK)	(1281)	DVSLVSLVANALGYSELGAIKSLRTLRALRPLRALSRFEG				
Translation of JeongAF225987	(1281)	DVSLVSLVANALGYSELGAIKSLRTLRALRPLRALSRFEG				
Consensus	(1281)	DVSLVSLVANALGYSELGAIKSLRTLRALRPLRALSRFEG				

Section 34

	(1321)	1321	1330	1340	1350	1360
ClareAJ251507protein	(1272)	MRVVVNALVGAIPSIMNVLLVCLIFWLIFSIMGVNLFAGK				
Translation of huNaIII18 (AK)	(1321)	MRVVVNALVGAIPSIMNVLLVCLIFWLIFSIMGVNLFAGK				
Translation of JeongAF225987	(1321)	MRVVVNALVGAIPSIMNVLLVCLIFWLIFSIMGVNLFAGK				
Consensus	(1321)	MRVVVNALVGAIPSIMNVLLVCLIFWLIFSIMGVNLFAGK				

Section 35

	(1361)	1361	1370	1380	1390	1400
ClareAJ251507protein	(1312)	FYHCVNMTTGNMFDISDVNNLSDCQALGKQARWKNVKVNF				
Translation of huNaIII18 (AK)	(1361)	FYHCVNMTTGNMFDISDVNNLSDCQALGKQARWKNVKVNF				
Translation of JeongAF225987	(1361)	FYHCVNMTTGNMFDISDVNNLSDCQALGKQARWKNVKVNF				
Consensus	(1361)	FYHCVNMTTGNMFDISDVNNLSDCQALGKQARWKNVKVNF				

Section 36

	(1401)	1401 1410 1420 1430 1440
ClareAJ251507protein	(1352)	DNVGAGYLALLQVATFKGWMDIMYAAVDSRDVKLQPVYEE
Translation of huNaIII18 (AK)	(1401)	DNVGAGYLALLQVATFKGWMDIMYAAVDSRDVKLQPVYEE
Translation of JeongAF225987	(1401)	DNVGAGYLALLQVATFKGWMDIMYAAVDSRDVKLQPVYEE
Consensus	(1401)	DNVGAGYLALLQVATFKGWMDIMYAAVDSRDVKLQPVYEE

Section 37

	(1441)	1441 1450 1460 1470 1480
ClareAJ251507protein	(1392)	NLYMYLYFVIFIIFGSFFTLNLFIGVIIDNFNQQKKKFGG
Translation of huNaIII18 (AK)	(1441)	NLYMYLYFVIFIIFGSFFTLNLFIGVIIDNFNQQKKKFGG
Translation of JeongAF225987	(1441)	NLYMYLYFVIFIIFGSFFTLNLFIGVIIDNFNQQKKKFGG
Consensus	(1441)	NLYMYLYFVIFIIFGSFFTLNLFIGVIIDNFNQQKKKFGG

Section 38

	(1481)	1481 1490 1500 1510 1520
ClareAJ251507protein	(1432)	QDIFMTEEQKKYYNAMKKLGSKKPQKPIPRPANKFQGMVF
Translation of huNaIII18 (AK)	(1481)	QDIFMTEEQKKYYNAMKKLGSKKPQKPIPRPANKFQGMVF
Translation of JeongAF225987	(1481)	QDIFMTEEQKKYYNAMKKLGSKKPQKPIPRPANKFQGMVF
Consensus	(1481)	QDIFMTEEQKKYYNAMKKLGSKKPQKPIPRPANKFQGMVF

Section 39

	(1521)	1521 1530 1540 1550 1560
ClareAJ251507protein	(1472)	DFVTRQVFDISIMILICLNMVTMMVETDDQGKYMTLVLSR
Translation of huNaIII18 (AK)	(1521)	DFVTRQVFDISIMILICLNMVTMMVETDDQGKYMTLVLSR
Translation of JeongAF225987	(1521)	DFVTRQVFDISIMILICLNMVTMMVETDDQGKYMTLVLSR
Consensus	(1521)	DFVTRQVFDISIMILICLNMVTMMVETDDQGKYMTLVLSR

Section 40

	(1561)	1561 1570 1580 1590 1600
ClareAJ251507protein	(1512)	INLVFIVLFTGEFVLKLVSLRHYYFTIGWNIFDFVVVILS
Translation of huNaIII18 (AK)	(1561)	INLVFIVLFTGEFVL[redacted]LVSLRHYYFTIGWNIFDFVVVILS
Translation of JeongAF225987	(1561)	INLVFIVLFTGEFVLKLVSLRHYYFTIGWNIFDFVVVILS
Consensus	(1561)	INLVFIVLFTGEFVLKLVSLRHYYFTIGWNIFDFVVVILS

Section 41

	(1601)	1601 1610 1620 1630 1640
ClareAJ251507protein	(1552)	IVGMFLAEMIEKYFVSPTLFRVIRLARIGRILRLIKGAKG
Translation of huNaIII18 (AK)	(1601)	IVGMFLAEMIEKYFVSPTLFRVIRLARIGRILRLIKGAKG
Translation of JeongAF225987	(1601)	IVGMFLAEMIEKYSVSPTLFRVIRLARIGRILRLIKGAKG
Consensus	(1601)	IVGMFLAEMIEKYFVSPTLFRVIRLARIGRILRLIKGAKG

Section 42

	(1641)	1641 1650 1660 1670 1680
ClareAJ251507protein	(1592)	IRTLLFALMMSLPALFNIGLLLFLVMFIYAIFGMSNFAYV
Translation of huNaIII18 (AK)	(1641)	IRTLLFALMMSLPALFNIGLLLFLVMFIYAIFGMSNFAYV
Translation of JeongAF225987	(1641)	IRTLLFALMMSLPALFNIGLLLFLVMFIYAIFGMSNFAYV
Consensus	(1641)	IRTLLFALMMSLPALFNIGLLLFLVMFIYAIFGMSNFAYV

Section 43

	(1681)	1681 ,1690 ,1700 ,1710 1720
ClareAJ251507protein	(1632)	KKEAGIDDMFNFETFGNSMICLFQITTSAGWDGLLAPILN
Translation of huNalII18 (AK)	(1681)	KKEAGIDDMFNFETFGNSMICLFQITTSAGWDGLLAPILN
Translation of JeongAF225987	(1681)	KKEAGIDDMFNFETFGNSMICLFQITTSAGWDGLLAPILN
Consensus	(1681)	KKEAGIDDMFNFETFGNSMICLFQITTSAGWDGLLAPILN

Section 44

	(1721)	1721 ,1730 ,1740 ,1750 1760
ClareAJ251507protein	(1672)	SAPPDCDPDTIHPGSSVKGDCGNPSVGIFFFVSYIIISFL
Translation of huNalII18 (AK)	(1721)	SAPPDCDPDTIHPGSSVKGDCGNPSVGIFFFVSYIIISFL
Translation of JeongAF225987	(1721)	SAPPDCDPDTIHPGSSVKGDRGDPSVGIFFFVSYIIISFL
Consensus	(1721)	SAPPDCDPDTIHPGSSVKGDCGNPSVGIFFFVSYIIISFL

Section 45

	(1761)	1761 ,1770 ,1780 ,1790 1800
ClareAJ251507protein	(1712)	VVVNMYIAVILENFSVATEESAEPLSEDDFEMFYEVWEKF
Translation of huNalII18 (AK)	(1761)	VVVNMYIAVILENFSVATEESAEPLSEDDFEMFYEVWEKF
Translation of JeongAF225987	(1761)	VVVNMYIAVILENFSVATEESAEPLSEDDFEMFYEVWEKF
Consensus	(1761)	VVVNMYIAVILENFSVATEESAEPLSEDDFEMFYEVWEKF

Section 46

	(1801)	1801 ,1810 ,1820 ,1830 1840
ClareAJ251507protein	(1752)	DPDATQFIEFSKLSDFAAALDPPLLIAKPNKVQLIAMDLP
Translation of huNalII18 (AK)	(1801)	DPDATQFIEFSKLSDFAAALDPPLLIAKPNKVQLIAMDLP
Translation of JeongAF225987	(1801)	DPDATQFIEFSKLSDFAAALDPPLLIAKPNKVQLIAMDLP
Consensus	(1801)	DPDATQFIEFSKLSDFAAALDPPLLIAKPNKVQLIAMDLP

Section 47

	(1841)	1841 ,1850 ,1860 ,1870 1880
ClareAJ251507protein	(1792)	MVSGDRIHCLDILFAFTKRVLGESGEMDALRIQMEDRFMA
Translation of huNalII18 (AK)	(1841)	MVSGDRIHCLDILFAFTKRVLGESGEMDALRIQMEDRFMA
Translation of JeongAF225987	(1841)	MVSGDRIHCLDILFAFTKRVLCESGEMDALRIQMEDRFMA
Consensus	(1841)	MVSGDRIHCLDILFAFTKRVLGESGEMDALRIQMEDRFMA

Section 48

	(1881)	1881 ,1890 ,1900 ,1910 1920
ClareAJ251507protein	(1832)	SNPSKVSYEPITTTLKRKQEEVSAAIIQRNFRCYLLKQRL
Translation of huNalII18 (AK)	(1881)	SNPSKVSYEPITTTLKRKQEEVSAAIIQRNFRCYLLKQRL
Translation of JeongAF225987	(1881)	SNPSKVSYEPITTTLKRKQEEVSAAIIQRNFRCYLLKQRL
Consensus	(1881)	SNPSKVSYEPITTTLKRKQEEVSAAIIQRNFRCYLLKQRL

Section 49

	(1921)	1921 ,1930 ,1940 ,1950 1960
ClareAJ251507protein	(1872)	KNISSNYNKEAIKGRIDLPIKQDMIIDKLNGNSTPEKTDG
Translation of huNalII18 (AK)	(1921)	KNISSNYNKEAIKGRIDLPIKQDMIIDKLNGNSTPEKTDG
Translation of JeongAF225987	(1921)	KNISSNYNKEAIKGRIDLPIKQDMIIDKLNGNSTPEKTDG
Consensus	(1921)	KNISSNYNKEAIKGRIDLPIKQDMIIDKLNGNSTPEKTDG

Section 50

		1961	1970	1980	1990	2000
ClareAJ251507protein	(1912)	SSSTTSPPSYDSVTKPDKEKFEKDKPEKESKGKEVRENQK				
Translation of huNalII18 (AK)	(1961)	SSSTTSPPSYDSVTKPDKEKFEKDKPEKESKGKEVRENQK				
Translation of JeongAF225987	(1961)	SSSTTPPPSYDSVTKPDKEKFEKDKPEKESKGKEVRENQK				
Consensus	(1961)	SSSTTSPPSYDSVTKPDKEKFEKDKPEKESKGKEVRENQK				

Figure 7